

**Estudio para la caracterización de pacientes con beneficio óptimo en el tratamiento de la insuficiencia mitral mediante el dispositivo MitraClip**

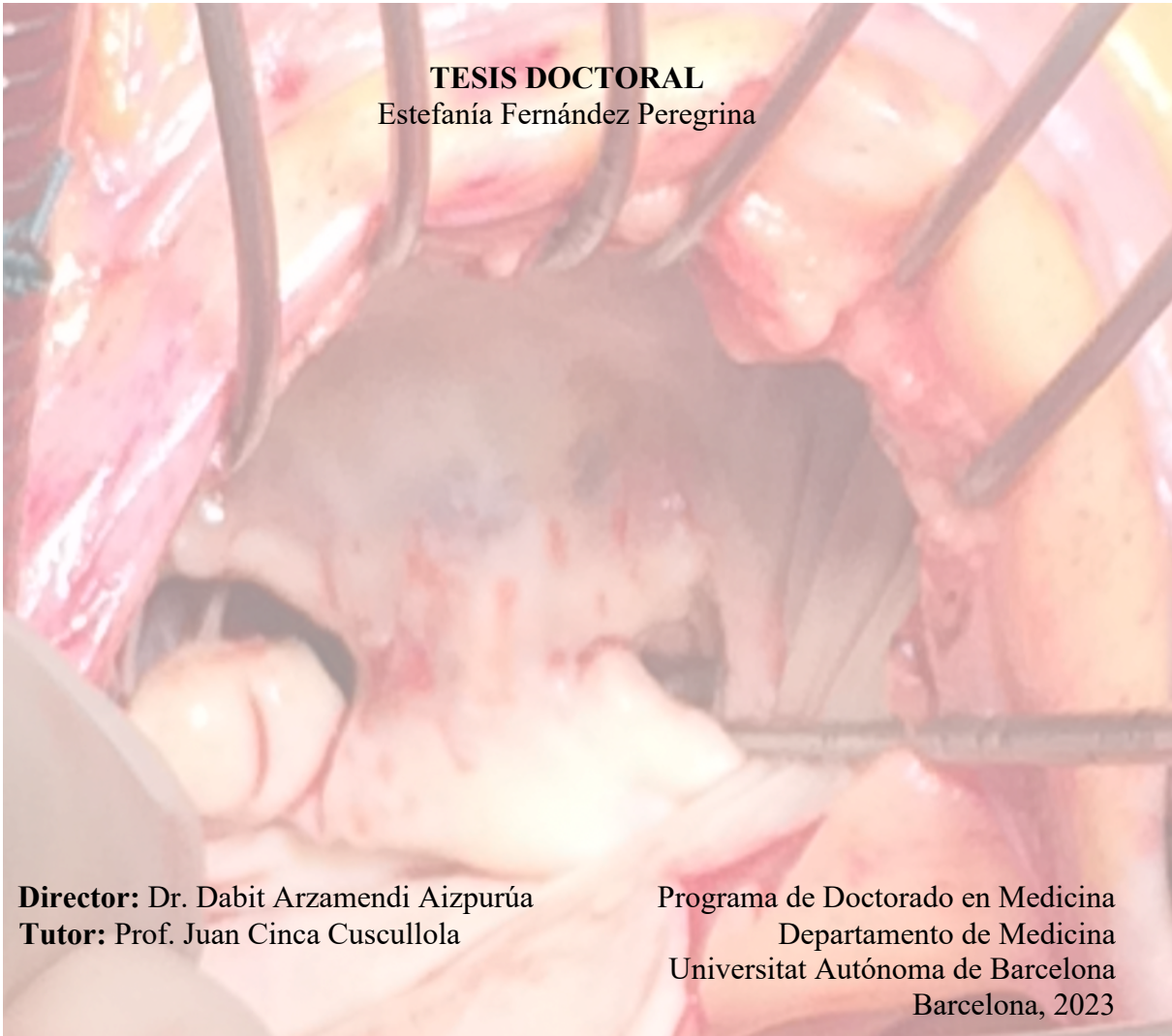
**Estefanía Fernández Peregrina**

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# **Estudio para la caracterización de pacientes con beneficio óptimo en el tratamiento de la insuficiencia mitral mediante el dispositivo MitraClip**



**TESIS DOCTORAL**  
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de Barcelona**







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“Individualmente, somos una gota. Juntos, somos un océano”

Ryunosuke Satoro







## LISTADO DE ABREVIATURAS

AI: Aurícula izquierda

DTSVI: Diámetro telesistólico de ventrículo izquierdo

ETE: Ecocardiografía transesofágica

EROA: Área de orificio regurgitante efectiva

FEVI: Fracción de eyección de ventrículo izquierdo

IAM: Infarto agudo de miocardio

IM: Insuficiencia mitral

IMD: Insuficiencia mitral degenerativa

IMF: Insuficiencia mitral funcional

PASP: Presión arterial sistólica pulmonar

MAC: *Mitral annulus calcification* (Calcificación del anillo mitral)

NYHA: New York Heart Association

RPBB: Reparación percutánea borde-a-borde

SGLVI: Strain global longitudinal de ventrículo izquierdo

VI: Ventrículo izquierdo

VTDVI: Volumen telediastólico de ventrículo izquierdo



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## RESUMEN

La Insuficiencia mitral es actualmente la segunda valvulopatía más frecuente en nuestro entorno. Sin tratamiento, la morbilidad y mortalidad asociada a esta entidad es alta. Una vez se instauran los síntomas o la valvulopatía se hace severa y con datos de mal pronóstico, se recomienda la reparación o recambio de la válvula. No obstante, para un gran número de pacientes, debido a la alta comorbilidad asociada, el tratamiento quirúrgico presenta un riesgo elevado.

La reparación mitral percutánea por aproximación de velos, surgió de la necesidad de ofrecer un tratamiento seguro y eficaz para aquellos pacientes con alto riesgo quirúrgico. En los últimos años, la experiencia adquirida y el diseño mejorado de los dispositivos disponibles, ha permitido ampliar su uso y mejorar los resultados de la intervención tanto a corto, como a medio plazo.

Sin embargo, en la actualidad, sigue siendo escasa la disponibilidad de datos que arrojen luz sobre los resultados de este tratamiento en anatomías consideradas “complejas”, clásicamente excluidas de la mayoría de estudios. Además, incluso en el caso de anatomías “favorables”, los estudios COAPT y MITRAFR, han destacado la necesidad de mejorar la selección de pacientes y el momento oportuno para maximizar la eficacia de esta técnica.

A través de un compendio de publicaciones, esta tesis doctoral presenta los resultados de la aplicación de esta técnica en anatomías o situaciones “complejas”, centrándose en particular en pacientes con calcificación del anillo mitral y en pacientes con disfunción ventricular severa.

El primer artículo de esta tesis examina los resultados clínicos y ecocardiográficos a corto y medio plazo de la terapia en una serie de pacientes consecutivos que presentan

calcificación del anillo mitral en un grado moderado o severo, y compara estos resultados con los de pacientes que no presentan dicha calcificación.

En el segundo artículo, se detallan los resultados de la aplicación de esta técnica en pacientes con disfunción ventricular severa, además de valorar la capacidad predictiva del análisis mediante strain global longitudinal de ventrículo izquierdo en este subgrupo de pacientes.

De este modo, se aportan nuevos datos que contribuyen a la caracterización de pacientes con beneficio óptimo para el tratamiento de la insuficiencia mitral mediante reparación percutánea.



## ABSTRACT

Mitral regurgitation is currently the second most frequent valve disease in our setting. Without treatment, the morbidity and mortality associated with this entity is high. Once symptoms develop or the valve disease becomes severe and/or associated with poor prognostic data, valve repair or replacement is recommended. However, for a large number of patients, due to the high associated comorbidity, surgical treatment presents a high risk.

Percutaneous mitral repair by leaflet approach arose from the need to offer a safe and effective treatment for patients deemed at high surgical risk. In recent years, the experience acquired and the improved design of the available devices have allowed its use to be extended and the results of the intervention to be improved both in the short and medium term.

However, nowadays, there are still few data available that shed light on the results of this treatment in anatomies considered "complex" which are classically excluded from most studies. Moreover, even in the case of "favorable" anatomies, the COAPT and MITRAFR studies have highlighted the need to improve patient selection and timing to maximize the efficacy of this technique.

Through a compendium of publications, this doctoral thesis presents the results of the application of this technique in "complex" anatomies or situations, focusing in particular on patients with mitral annulus calcification and patients with severe ventricular dysfunction.

The first article of this thesis examines the short- and medium-term clinical and echocardiographic results of the therapy in a series of consecutive patients with

moderate to severe mitral annulus calcification, and compares these results with those of patients without such calcification.

In the second article, the results of the application of this technique in patients with severe ventricular dysfunction are detailed, in addition to assessing the predictive capacity of analysis by longitudinal global strain of the left ventricle in this subgroup of patients.

Thus, new data are provided that can contribute to the characterization of patients with optimal benefit for the treatment of mitral regurgitation by percutaneous repair.

# 1.INTRODUCCIÓN



## 1.1. La insuficiencia mitral

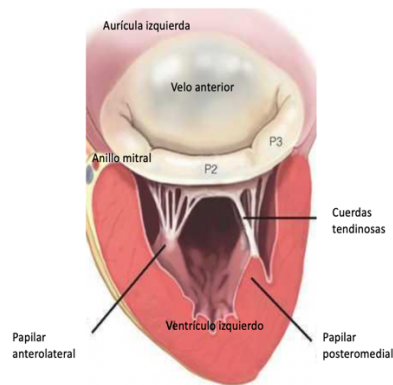
### 1.1.1. Anatomía valvular mitral.

La válvula mitral, o auriculo-ventricular izquierda, permite el flujo sanguíneo hacia el ventrículo izquierdo (VI) durante la diástole y sella la aurícula izquierda (AI) durante la sístole. Se trata de un complejo aparato (*Figura 1*) formado por:

- Dos *valvas* o *velos* que son gruesas en la zona de inserción y en su borde libre (o segmento de coaptación), siendo más finas en su segmento medio. En condiciones normales presentan un grosor de aproximadamente 1mm y una longitud de entre 5 y 10 mm, así como una razón de área valvar/anillo mitral de 1.5-2.0 y una altura de coaptación de aproximadamente 8mm. Histológicamente se componen de tres capas: ventricular (fibrosa), media (esponjosa, con menor fibrina) y auricular (con mayor colágeno y elastina). En la nomenclatura clásica o de Carpentier (1) el velo anterior se denomina A y el posterior P dividiéndose cada uno en tres festones siendo los segmentos A1-P1 los más laterales (próximos a la orejuela) y A3-P3 los más mediales (próximos al septum). El velo anterior es más móvil, largo y grueso y con pocas o ninguna indentación, al contrario que el velo posterior (2).
- Un *anillo* fibroelástico con morfología en silla de montar donde se ancla la válvula mitral. Su porción anterior se continúa con el anillo aórtico siendo una zona más rígida mientras que la porción posterior de éste es más flexible, permitiendo el movimiento y siendo el lugar donde se pueden producir la mayoría fenómenos de calcificación y dilatación anular (2,3). Durante la sístole,

debido a contracción anteroposterior, presenta una forma elíptica, aproximando los velos y ayudando al cierre valvular. En la diástole, presenta una forma esférica alcanzando su mayor área, que en condiciones normales se encuentra entre 5 y 11 mm<sup>2</sup> (4).

- *Cuerdas tendinosas* fibroelásticas que se originan en los músculos papilares y se insertan en las valvas. Las cuerdas primarias o marginales son finas y se insertan en la punta del velo evitando el prolapso mientras que las cuerdas secundarias o basales son gruesas y se insertan en el cuerpo de la valva para su anclaje (5).
- Dos *músculos papilares*: el anterolateral, que recibe una doble irrigación a través de la primera marginal y la diagonal, y el posteromedial, que es irrigado por un único vaso (generalmente la coronaria derecha, si bien en ocasiones por un ramo marginal) (6). La contracción longitudinal ventricular los acerca al anillo, lo que a su vez aproxima los velos a la cara auricular ayudando al cierre valvular inicial. Además, la contracción del propio papilar mantiene la tensión entre ellos y los velos y previene la obstrucción del tracto de salida por el velo anterior.
- Las paredes del *ventrículo izquierdo* donde se insertan los músculos papilares. Cualquier alteración en su geometría puede desplazar los músculos papilares y provocar insuficiencia (7).
- Las paredes de la *aurícula izquierda*: si bien clásicamente no se incluye como parte general del aparato mitral, la dilatación de la AI puede contribuir a la aparición de insuficiencia mitral principalmente por afectación de velo posterior debido a la continuidad del músculo auricular con éste (8).



**Figura 1.** Aparato valvular mitral: componentes. Adaptado con permiso de Castillo et al (9)

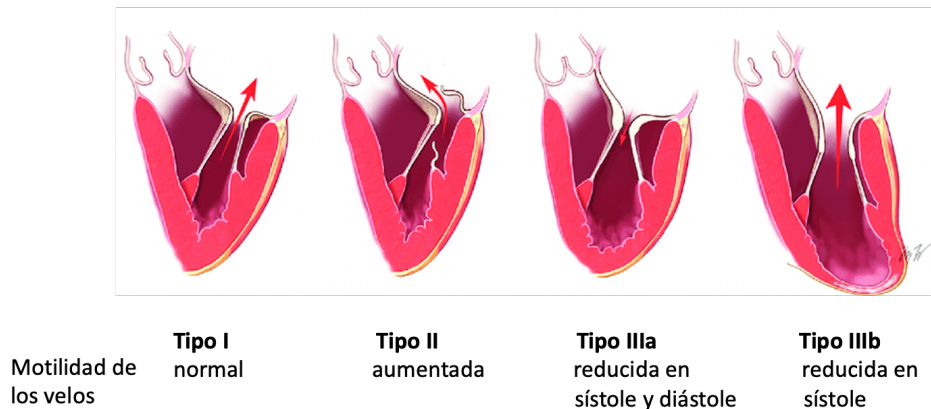
### 1.1.1. Prevalencia y etiología

La incompetencia o insuficiencia mitral (IM) es la incapacidad del cierre de la válvula, lo que ocasiona un flujo retrógrado de sangre desde el ventrículo a la aurícula izquierda. Esta afección se origina debido a alteraciones en cualquiera de sus componentes, desde los velos hasta la pared muscular ventricular (13,14). Tradicionalmente, la insuficiencia mitral se clasifica en tres tipos según la movilidad de los velos (1):

Tipo I: En este tipo, la movilidad de las valvas es normal y puede deberse a factores como la perforación de valva o la dilatación anular.

Tipo II: En este grupo, se observa un exceso de movilidad de las valvas secundaria a elongación de cuerdas y prolapso que puede asociarse a rotura de cuerdas y eversión del velo (*flail*).

Tipo III: En este caso, existe una restricción del movimiento de las valvas que coaptan por debajo del plano anular debido a la retracción del aparato subvalvular (IIIa) o al desplazamiento de músculo papilar, lo que provoca a su vez el desplazamiento apical o *tethering* de la valva (IIIb) (Figura 2).



**Figura 2.** Clasificación de la insuficiencia mitral según Carpentier. Adaptado con permiso de Stone et al (15)

No obstante, existe otra clasificación que cataloga la insuficiencia mitral en dos categorías principales (16):

- Degenerativa o primaria (IMD), debida a anormalidades intrínsecas en el aparato valvular como el prolapso valvular, hendidura mitral, enfermedad reumática, radiación, enfermedad de tejido conectivo, etc.
- Funcional o secundaria (IMF), originada por la dilatación del anillo secundario a dilatación ventricular o atrial que puede estar asociada a cardiomiopatía o a cambios en el aparato subvalvular (17,18). Habitualmente la dilatación del anillo por sí sola no provoca una IM severa en estadios iniciales debido a la relación entre el área de los velos y del anillo mitral, lo que asegura suficiente tejido para el cierre valvular. Además, la acción coordinada de papilares y cuerdas tendinosas compensa dicha dilatación. Sin embargo, a medida que la



dilatación progresa o la patología miocárdica subyacente empeora, los mecanismos de compensación se vuelven insuficientes (19).

Es importante destacar que, en ocasiones, pueden coexistir características propias de ambos grupos en un mismo paciente.

La IM, que actualmente es la segunda valvulopatía más común en Europa (10–12), está experimentando un aumento en su prevalencia debido al envejecimiento demográfico y al aumento de la esperanza de vida. Actualmente en países desarrollados la IM tiene como causa principal la degeneración, seguida de la enfermedad isquémica (12). Por un lado, en la causa degenerativa destacan dos subgrupos: la enfermedad fibroelástica y la enfermedad de Barlow. La primera afecta principalmente a pacientes mayores de 60 años. En esta condición, se produce un debilitamiento, elongación y rotura de las cuerdas tendinosas debido a un déficit de fibrilina. La enfermedad de Barlow, por su parte, afecta a pacientes jóvenes y se caracteriza por valvas mixomatosas, con tejido redundante y prolapsos asociados (20). Por otro lado, en la causa isquémica podemos distinguir también dos tipos según el momento de presentación clínica. La forma aguda, que se produce por rotura de músculo papilar; y la forma crónica, que resulta del remodelado de VI con desplazamiento de los papilares apical (generando *tenting* simétrico y jet de regurgitación central) o inferior (generando *tenting* asimétrico y jet de regurgitación excéntrico). También influye en esta forma la dilatación del anillo y pérdida de la contracción anular sistólica (7,17,21).

### 1.1.2. Diagnóstico

#### *Clínica*

La sintomatología más común de la IM es la disnea, cuya gravedad y síntomas concomitantes depende de la severidad y velocidad de la progresión de la valvulopatía, el estado volémico del paciente y la presencia o ausencia de cardiomiopatía o taquiarritmia asociada. Del mismo modo, en la exploración física se pueden observar signos relacionados tanto con la patología subyacente como con la etiología y gravedad de la IM.

El hallazgo más destacado en la exploración física es la presencia de un soplo sistólico, que puede variar ligeramente según la causa subyacente y la duración de la afección: puede ser holosistólico en el caso de una IM funcional crónica y severa, telesistólico en prolapso valvular puro, o prácticamente imperceptible en IM aguda.

#### *Ecocardiografía*

La ecocardiografía es la técnica de imagen principal en el estudio de la IM, ya que resulta fundamental para determinar la etiología, severidad y consecuencias cardíacas de la misma. Además, permite evaluar posibles valvulopatías asociadas y la función biventricular (22–24).

La gradación de la insuficiencia mitral se basa en una combinación de métodos cualitativos y cuantitativos. Se considera severa cuando presenta los siguientes parámetros:

- Vena contracta  $\geq 7\text{mm}$
- Fracción de regurgitación  $\geq 50\%$
- Área del orificio regurgitante efectivo (EROA)  $\geq 40\text{mm}^2$

- Volumen regurgitante  $\geq 60$  ml

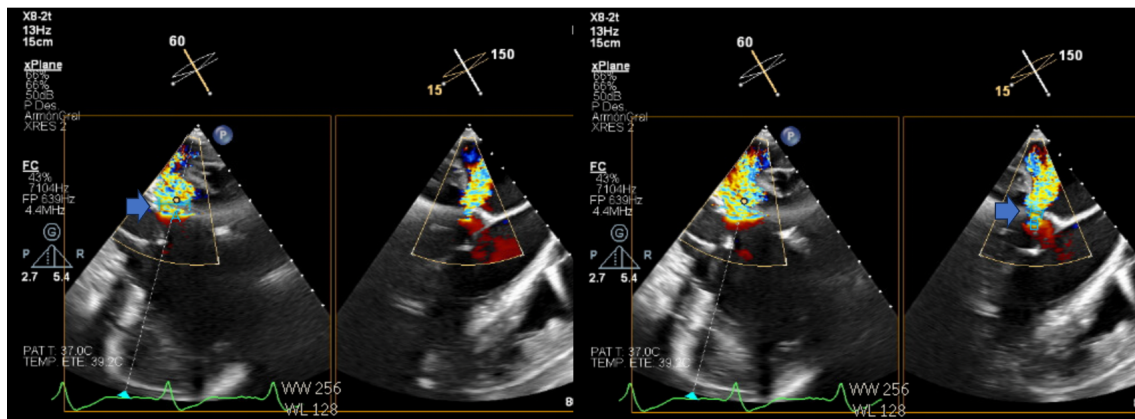
Sin embargo, es importante destacar que en casos con anillos mitrales más elípticos o en situaciones de disfunción ventricular, se podrían considerar umbrales inferiores como significativos (EROA  $\geq 30\text{mm}^2$  y volumen regurgitante  $\geq 45$  ml) (*Tabla 1*).

|                                                                              | Ligera            | Moderada                      | Severa                                                         |
|------------------------------------------------------------------------------|-------------------|-------------------------------|----------------------------------------------------------------|
| <b>Morfología valvular</b>                                                   | Normal/anormal    | Normal/anormal                | Flail / ruptura músculo papilar/<br>perforación                |
| <b>Flujo color del jet de IM</b>                                             | Pequeño central   | Intermedio                    | Jet central grande (>50% AI) o excéntrico<br>con efecto Coanda |
| <b>Zona de convergencia de flujo<sup>a</sup></b>                             | Ausente o pequeño | Intermedio                    | Grande (holosistólica)                                         |
| <b>Señal de CW del jet de IM</b>                                             | Débil/parabólico  | Densa/parabólico              | Densa/Triangular                                               |
| <b>Ancho de VC (mm)</b>                                                      | <3                | 3-7                           | >7 (>8 para biplano)                                           |
| <b>Flujo de vena pulmonar</b>                                                | Dominancia onda S | Reducción onda S <sup>b</sup> | Inversión onda S                                               |
| <b>Flujo Mitral</b>                                                          | Dominancia onda A | Variable                      | Dominancia onda E(1.5 m/seg) <sup>c</sup>                      |
| <b>VTi mit/ VTI Ao</b>                                                       | <1                | 1-1.4                         | > 1,4                                                          |
| <b>EROA (mm<sup>2</sup>)</b>                                                 | <20               | 20-29; 30-39 <sup>d</sup>     | >40 IMD y $\geq 30$ IMF                                        |
| <b>R Vol (mL)</b>                                                            | <30               | 30-44; 45-59 <sup>f</sup>     | >60 IMD y $\geq 45$ IMF                                        |
| <b>Fracción regurgitante (%)</b>                                             | <30               | 30-40;41-50                   | >50                                                            |
| <b>Tamaño de VI y AI y presión sistólica en arteria pulmonar<sup>d</sup></b> |                   |                               |                                                                |

**Tabla 1.** Gradación de la insuficiencia mitral por ecocardiografía. AI: aurícula izquierda. CW: Doppler continuo. EROA: Área de orificio regurgitante efectivo. IM: Insuficiencia Mitral. IMD: Insuficiencia mitral degenerativa. IMF: Insuficiencia mitral funcional. RVol: volumen regurgitante. VI: Ventrículo izquierdo. Vc: Vena contracta. a) A un límite Nyquist de 50-60 cm/seg. b) Sin otra causa de reducción de onda S (fibrilación auricular, elevación de presión en AI) c) En ausencia de otras causas de presión elevada en AI y de estenosis mitral. d) Excepto por otras causas, el tamaño del VI y AI y la presión pulmonar son normales en pacientes con IM leve. En IM severa aguda la presión pulmonar está usualmente elevada mientras que el tamaño del VI suele ser normal. En IM severa crónica el VI está clásicamente dilatado.

Es fundamental prestar especial interés en la evaluación de condiciones que pueden influir en la gradación de la IM tales como la volemia del paciente, el ritmo cardíaco, la terapia farmacológica y la viabilidad miocárdica. Asimismo, en ocasiones dicha

gradación puede resultar dificultada por la presencia de múltiples flujos o jets de regurgitación o por la presencia de anillos mitrales con la característica forma elíptica. En estas ocasiones se considera más fiable la determinación de la vena contracta mediante planimetría con biplano (*Figura 3*) o con planimetría directa con ecocardiografía 3D.

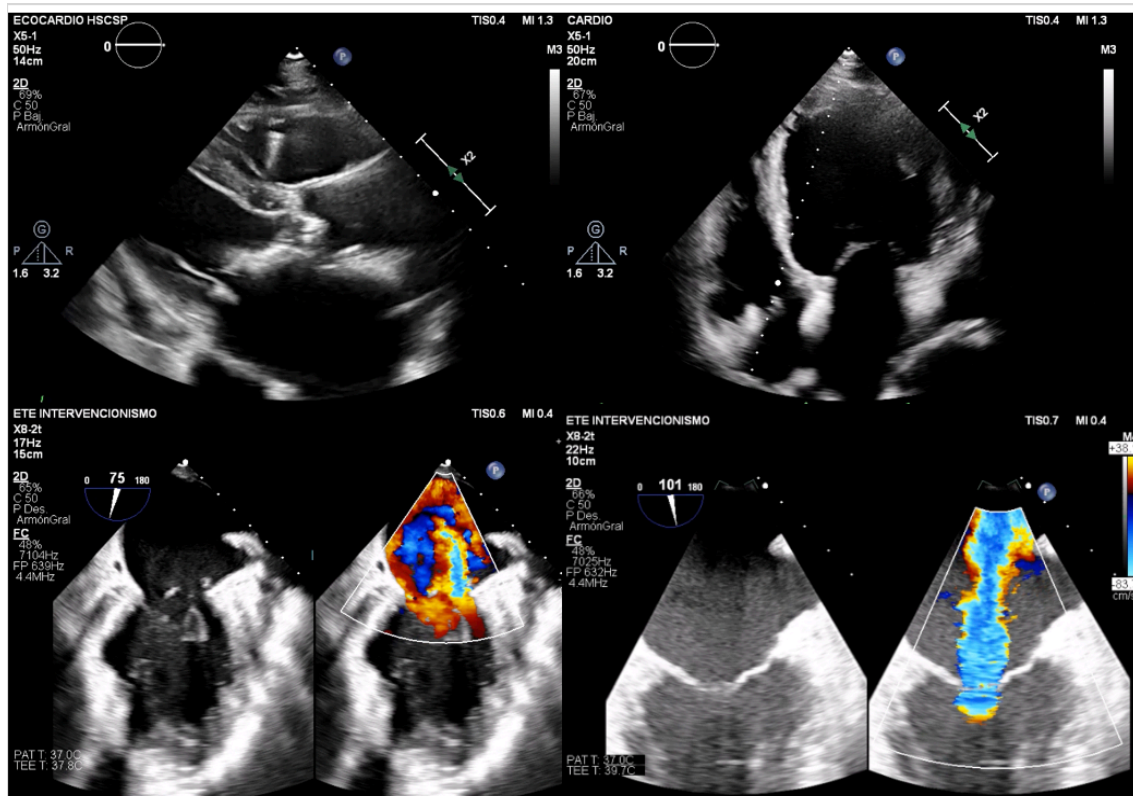


**Figura 3.** Planimetría de vena contracta en insuficiencia mitral con ayuda de biplano: A la izquierda, medida de la vena contracta desde plano intercomisural; a la derecha, medida de la vena contracta en plano de tracto de salida de ventrículo izquierdo.

Además del grado de severidad de la IM, la ecocardiografía proporciona información anatómica crucial. En el caso de IMD es esencial la evaluación del sustrato anatómico de la patología, su localización, la presencia y extensión de calcificación anular y el tamaño anular. Esta información permite estimar la posibilidad de reparación, evaluar el riesgo de inducir estenosis valvular durante la misma y determinar la necesidad de añadir un anillo protético en casos quirúrgicos.

Por otro lado, en el caso de IMF, se ha de prestar además especial atención a la función ventricular y a parámetros como la profundidad de coaptación y al área de *tenting*

(figura 4). Estos datos son fundamentales para una evaluación completa y para la toma de decisiones clínicas.



**Figura 4.** Ejemplo de diversas etiologías de insuficiencia mitral: en imagen superior izquierda, se puede observar una válvula mitral con calcificación severa de anillo que se extiende a velos; en imagen superior derecha, se muestra un ventrículo izquierdo dilatado que condiciona dilatación anular mitral; en imagen inferior izquierda, se puede constatar ruptura de músculo papilar que conlleva asociada una insuficiencia mitral masiva aguda; y en la imagen inferior derecha, se muestra una válvula mitral con insuficiencia severa por dilatación del anillo y tenting bivalvar.

La ecocardiografía no sólo desempeña un papel fundamental en el diagnóstico de esta patología, sino que también resulta esencial en la selección del tratamiento, así como en la monitorización y guía durante el procedimiento y seguimiento posterior (25–28) .

La evaluación minuciosa de la válvula mitral permite determinar la idoneidad de cada enfoque de corrección, ya sea quirúrgico o percutáneo, para cada paciente. Por ejemplo, en casos de IM causada por la rotura de cuerdas, las técnicas de anuloplastia pueden no ser la mejor opción, y los *flails* amplios podrían presentar desafíos en su corrección mediante terapias borde-a-borde (Tabla 2).

|                                                      | Lesiones simples                                                               | Lesiones complejas                                                                                                                                  | Lesiones con alto riesgo de fracaso de reparación                                                                                                                                |
|------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Tipo de lesión</b>                                | Prolapso o flail de velo posterior<br>Dilatación anular<br>Perforación de velo | Lesiones complejas de velo posterior<br>Prolapso o flail anterior<br>Prolapso o flail de ambos velos<br>Lesiones combinadas<br>Anomalías anatómicas | Prolapso con calcificación anular extensa<br>Prolapso con hipoplasia de velo contralateral<br>Deficiencia fibroelástica severa<br>Daño post-endocarditis<br>Enfermedad reumática |
| <b>Probabilidad de reparación exitosa y duradera</b> | Alta                                                                           | Dependiente de experiencia del equipo quirúrgico                                                                                                    | Baja                                                                                                                                                                             |
| <b>Experiencia quirúrgica necesaria</b>              | Baja                                                                           | Alta                                                                                                                                                | Muy alta                                                                                                                                                                         |

**Tabla 2.** Clasificación de las distintas lesiones valvulares mitrales y su posibilidad de reparación. Modificado de Alfieri et al (29)

En cuanto a la guía del procedimiento, la ecocardiografía transesofágica (ETE) es una herramienta esencial. Es crucial para la realización de la punción transeptal, cuando ésta se requiere en técnicas percutáneas, así como para el seguimiento de la progresión de los dispositivos y la valoración del grado de IM residual tras la reparación inicial. Esta evaluación de la insuficiencia mitral residual también es fundamental para determinar si se necesitan otras técnicas para lograr un resultado final óptimo. Además, la monitorización mediante ETE permite la detección de forma temprana de posibles complicaciones, como el implante inadecuado de un dispositivo, lesión de estructuras vecinas, aparición de derrame pericárdico o el desarrollo de estenosis valvular (30,31).

*Modalidades accesorias para el diagnóstico de la insuficiencia mitral:*

Otras modalidades diagnósticas pueden contribuir a establecer el estado general del paciente y el impacto de la valvulopatía, así como a orientar en la determinación del momento adecuado para el tratamiento y la selección del tipo de intervención invasivo. El cateterismo cardíaco derecho, por ejemplo, proporciona información sobre el estado volémico, la función cardíaca y la posible coexistencia y gravedad de la hipertensión pulmonar (32,33) (*Figura 5*).



**Figura 5.** Cateterismo cardíaco derecho en paciente con insuficiencia mitral. A la izquierda, registro de presión enclavada pulmonar donde se observa onda v prominente típica de este tipo de valvulopatía; en imagen central, registro de presiones pulmonares arteriales; a la derecha, registro de presiones ventriculares derechas.

Otros exámenes que pueden ayudar a discernir la gravedad de la IM en casos de discrepancia entre los parámetros ecocardiográficos, así como a evaluar las dimensiones y la función de las distintas cámaras cardíacas, son la resonancia cardíaca magnética (34) y la ecocardiografía de estrés (32). Además, la tomografía cardíaca puede proporcionar información valiosa para la evaluación del tamaño de anillo mitral y su relación con estructuras circundantes, lo que resulta esencial para considerar técnicas de anuloplastia o reemplazo valvular (35). Desde un punto de vista analítico, el parámetro

más estudiado para diagnóstico, seguimiento y estratificación pronóstica es el NT-proBNP o Propéptido natriurético cerebral N-terminal (36–38).

### 1.1.3. Tratamiento y pronóstico

Sin tratamiento, la evolución natural de la IM grave crónica conlleva una tasa de mortalidad del 70% a 5 años (39), siendo este pronóstico aún más desfavorable en el caso de IMF (40,41). La decisión terapéutica ha de ser individualizada y valorada de manera integral por un equipo médico multidisciplinario que tome en consideración factores como la sintomatología del paciente, las comorbilidades, la anatomía valvular y las opciones técnicas disponibles, así como la opinión informada del paciente.

El *tratamiento médico* busca paliar los síntomas y se basa en la reducción de la postcarga en casos de IM aguda mediante el uso de diuréticos y nitratos. En el caso de formas crónicas, se mantiene la terapia médica recomendada para insuficiencia cardíaca crónica, que incluye el uso de betabloqueantes, inhibidores de la enzima convertidora de angiotensina, bloqueadores del receptor de angiotensina e inhibidores de la neprilisina (16,42).

La *intervención quirúrgica* está indicada en pacientes sintomáticos con IMD severa y riesgo quirúrgico aceptable, según la evaluación del equipo multidisciplinario. También se considera en pacientes asintomáticos pero que presenten datos de mal pronóstico como disfunción ventricular izquierda entendida como FEVI  $\leq 60\%$ , diámetro telesistólico de ventrículo izquierdo  $\geq 40\text{mm}$ , volumen auricular izquierdo  $\geq 60\text{ml}$  o

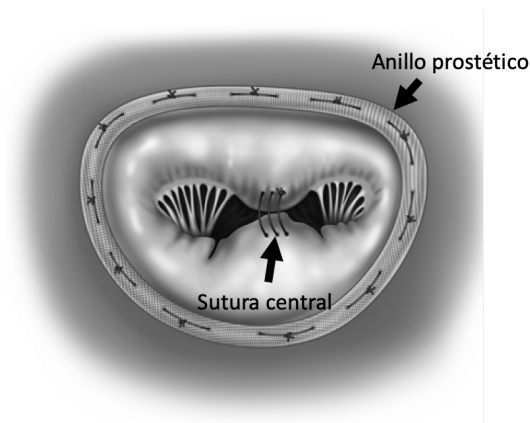


presión pulmonar arterial sistólica >50mmHg o fibrilación auricular. Por otro lado, la intervención quirúrgica en etiologías secundarias es más cuestionada (43) y sólo se recomienda en aquellos pacientes que precisan cirugía de revascularización miocárdica u otro tipo de cirugía cardíaca debido al alto riesgo quirúrgico que estos pacientes presentan y la ausencia de beneficio probado, junto con una alta tasa de recurrencia (44). Si bien existen varias técnicas quirúrgicas, se recomienda favorecer la reparación sobre la sustitución valvular, principalmente en casos de IMD (16,45), mientras que en casos de IMF, que pueden tener una mayor tasa de recurrencia, esta decisión es más discutida (46).

No obstante, existe un grupo de pacientes que presentan ciertas características como la edad avanzada y comorbilidades que los hacen candidatos subóptimos o prohibitivos a la cirugía por alto riesgo. Para ellos, el tratamiento percutáneo podría suponer una solución a su problema médico.

## **1.2. Tratamiento transcatéter de la insuficiencia mitral**

En el año 1991, el Dr. O. Alfieri realizó una observación interesante durante una cirugía de corrección de defecto septal interatrial. Encontró una anomalía congénita consistente en una válvula mitral de doble orificio que, no obstante, era normofuncionante. Esta observación condujo a la posterior realización de una reparación el mismo día en otro paciente afecto de insuficiencia mitral severa por prolapso de velo anterior mediante la sutura de la porción prolapsante y la porción de velo posterior enfrentada a la misma, creando de este modo un doble orificio, junto con la adición de anillo prostético (29) (*Figura 6*).



**Figura 6.** Cirugía de Alfieri. Modificada con permiso de Alfieri et al (29)

Posteriormente, esta técnica ha evolucionado para adaptarse a los resultados observados y a la anatomía de cada paciente. La sutura debe realizarse en la zona donde se origina el flujo de insuficiencia y ajustarse al grosor de velos (puede reforzarse con *pledges* de teflón en casos de velos finos), considerando asimismo la cantidad de velo prolapsante.

El objetivo es tratar la insuficiencia de manera efectiva al mismo tiempo que se garantiza que el área valvular efectiva no sea restrictiva. En la mayoría de los casos, se incorpora un anillo prostético para aumentar la superficie de coaptación, reducir la tensión en la sutura y prevenir la posible dilatación del anillo (29,47–49).

Estudios computacionales posteriores demostraron que, desde una perspectiva hemodinámica, las válvulas de doble orificio funcionan de manera similar a las que presentan un único orificio (50). El área efectiva total equivale a la suma de las áreas de ambos orificios, con velocidades y gradientes transvalvulares independientes a la conformación de éstos. Además, estos gradientes son consistentes, independientemente del lugar de medición, lo que facilita la estimación de los resultados obtenidos.

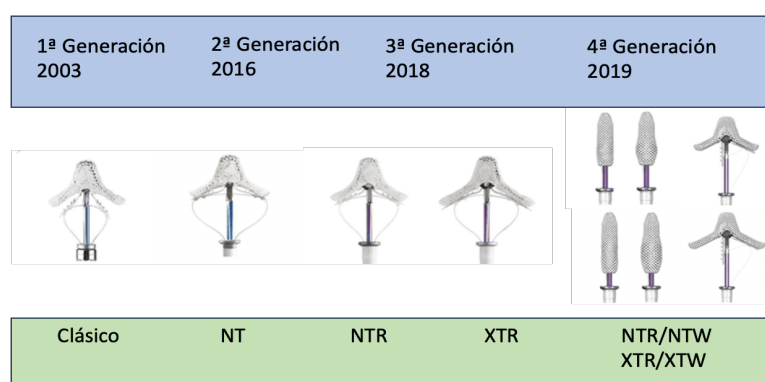
Los prometedores datos iniciales (51), junto con la reproducibilidad de la técnica, su simplicidad y versatilidad. llevaron a una rápida adopción en la comunidad quirúrgica y a al desarrollo de una versión percutánea (52).

### 1.2.1. Reparación percutánea borde-a-borde: descripción de la técnica

El tratamiento percutáneo de reparación borde-a-borde (RPBB) reproduce la técnica de Alfieri de plicatura de velos y se ha consolidado como una alternativa a la cirugía en insuficiencia mitral de causa primaria con alto riesgo quirúrgico (53–55), así como en casos seleccionados de insuficiencia de causa secundaria (56,57).

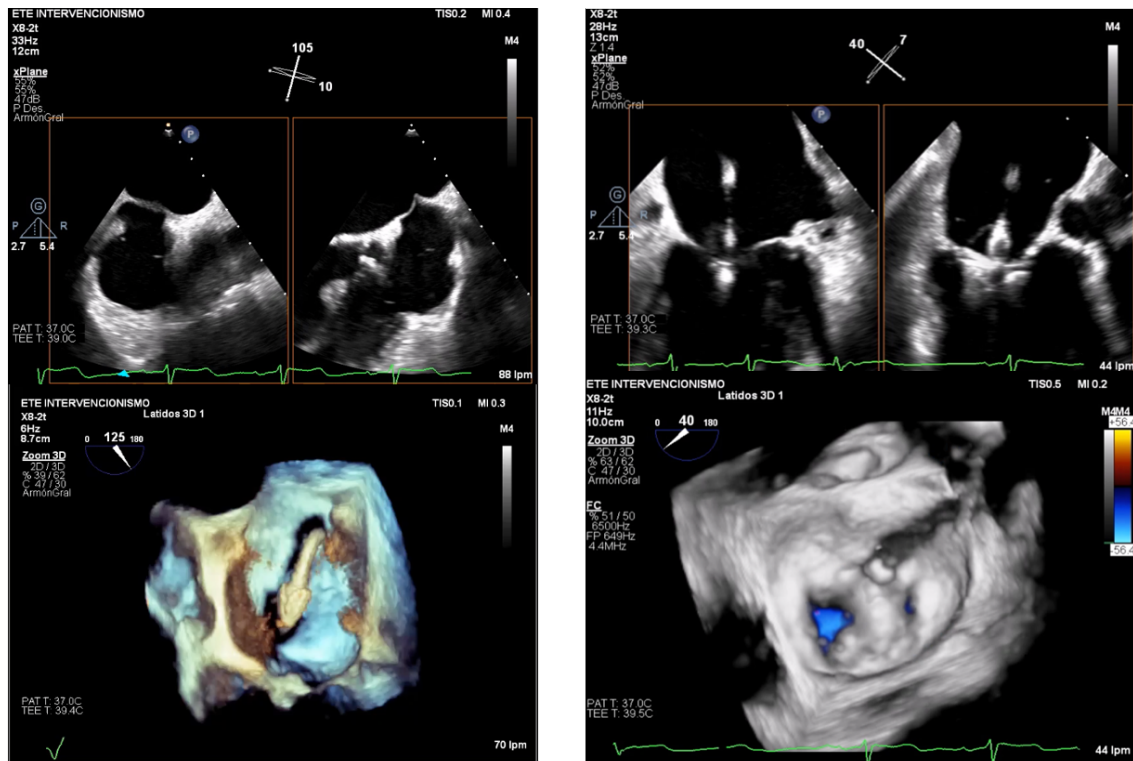
Actualmente el dispositivo más empleado para la reparación mitral borde-a-borde mediante abordaje transcatéter es el MitraClip (Abbott Laboratories, Menlo Park, California, USA) que ha sido utilizado en más de 150.000 pacientes en todo el mundo desde que obtuviera el marcado CE en 2008 para IM primaria y en 2019 para IM secundaria (33,58).

El dispositivo consta de dos brazos (“clips”) fabricados en cromo-cobalto con “grippers” flexibles de nitinol que presentan 4 (NT/NTW) o 6 (XT o XTW) elementos de fricción longitudinal, lo que les permite la captura de tejido valvular. Desde 2020, se encuentra disponible una cuarta generación con 4 tamaños diferentes atendiendo al grosor y longitud de los clips: NT con 4mm de grosor y 9mm de longitud, NTW con 6mm de grosor y 9 mm de longitud, XT con 4 mm de grosor y 12 mm de longitud y XTW con 6mm de grosor y 12 mm de longitud (*Figura 7*).



**Figura 7.** Evolución del dispositivo MitraClip.

Los clips se avanzan con ayuda de un catéter que permite la deflexión anterior/posterior, medial/lateral y anteroposterior del mismo. El procedimiento se realiza generalmente bajo anestesia general siendo guiado por escopia y por ETE (*Figura 8*).

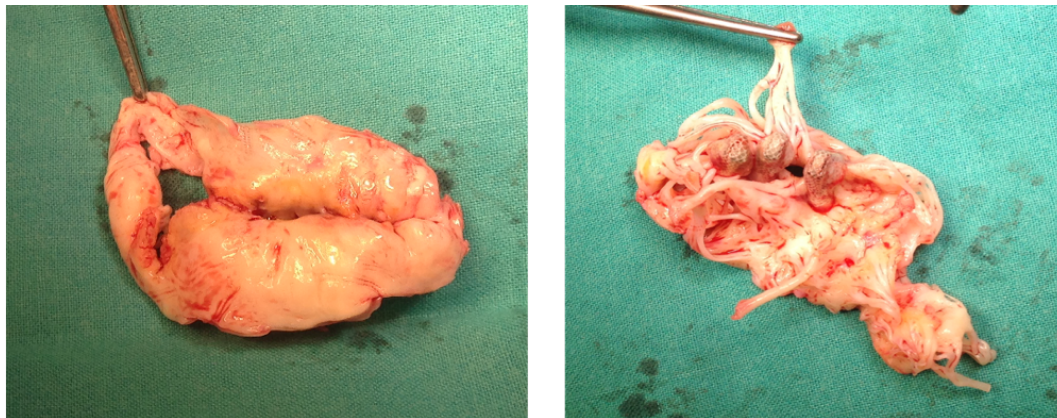


**Figura 8.** Monitorización ecocardiográfica de la terapia borde-a-borde. Esquina superior izquierda, monitorización de punción transeptal; esquina inferior izquierda, avance del sistema y dispositivo en aurícula izquierda; esquina superior derecha, monitorización de la captura de velos en biplano; esquina inferior derecha, monitorización de la captura de velos y efecto en reducción del grado de insuficiencia mitral.

A través de un acceso venoso femoral, se realiza una punción transeptal de localización posterior y superior. Sin embargo, el punto óptimo de punción será determinado por la propia lesión valvular (en casos de degeneración valvular se pueden requerir punciones ligeramente más superiores mientras que en casos de IMF, en los que el plano de coaptación habitualmente es inferior al plano del anillo mitral, la punción suele ser

ligeramente inferior) (59). Una vez se ha realizado la punción transeptal se avanza una guía de alto soporte hasta la vena pulmonar y sobre ésta, se progresa el catéter guía del sistema MitraClip de 24 french. A través de este catéter, se introduce el clip seleccionado según la anatomía de la válvula y de la propia regurgitación. Una vez que el clip se encuentra perpendicular al flujo o jet de regurgitación y coaxial a éste, se avanza hacia ventrículo con las palas y *grippers* abiertos. Se verifica la orientación del clip y se retrae hasta capturar los velos al cerrar el dispositivo, aproximando así ambos velos. Si la reducción del grado de insuficiencia se considera satisfactoria según la ecocardiografía, se procede a la liberación del clip. Además, la aproximación de velos genera una cierta reducción del diámetro del anillo antero-posterior, logrando un efecto ligero de anuloplastia mitral añadido.

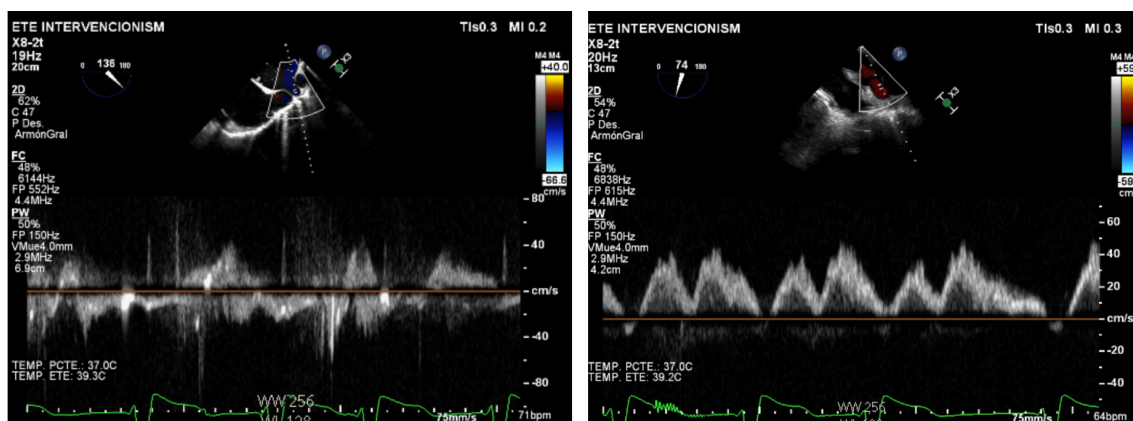
Se pueden implantar varios dispositivos si se considera necesario por amplitud del jet de regurgitación, existencia de varios jets o reducción parcial de la IM (*Figura 9*).



**Figura 9.** Pieza anatomopatológica, válvula mitral con tres dispositivos MitraClip implantados en A2P2. A la izquierda, vista desde cara auricular. A la derecha, vista desde cara ventricular. Imágenes cedidas por Dr. Taurón.

Asimismo, con la cuarta generación de este clip, se puede realizar la captura de velos de forma individual. Esto permite que, si tras la captura simultánea de ambos velos se observa un resultado subóptimo debido a que uno de los velos no se ha insertado lo suficientemente profundo, sea posible abrir el *gripper* de ese velo y volver a recapturarlo. En ocasiones esto puede requerir una ligera rotación del dispositivo para lograr una mayor profundidad y coaxialidad, lo que optimiza el implante y reduce el grado de insuficiencia residual.

Durante el implante, es importante evaluar cuidadosamente la magnitud de la IM residual y el gradiente transvalvular, ya que estos parámetros tienen valor pronóstico (60,61). No obstante, es necesario tener en cuenta que después de la implantación del clip, se crean múltiples orificios de geometría irregular, dependiendo de cuántos clips se hayan implantado, y que el propio dispositivo puede crear una sombra acústica que dificulta la determinación precisa de la IM residual mediante métodos convencionales (62). Por ello, se recomienda la valoración adicional de las curvas de flujo en las venas pulmonares pre y post procedimiento mediante ecocardiografía o la medición invasiva de la onda v auricular invasiva (23,63,64) (*Figura 10*).



**Figura 10.** Morfología de venas pulmonares en paciente con insuficiencia mitral severa previo a reparación mitral percutánea borde-a-borde (izquierda) y posterior a ella (derecha). Previo a la

intervención, se observa inversión de sistólica del flujo en venas pulmonares que normaliza tras la reparación.

En caso de IM residual moderada o severa o en casos de fracaso del implante por desprendimiento de uno de los velos, puede ser necesario el implante de otro clip (o reintervención si esta situación se constata en el seguimiento) (65).

#### 1.2.2. Evidencia para la reparación mitral mediante la terapia borde-a-borde

El primer estudio que evaluó la seguridad y eficacia de esta técnica fue el EVEREST (Endovascular Valve Edge-to-Edge Study) (66). Publicado en 2009, se trató de un estudio cuyo objetivo era la valoración de la seguridad y viabilidad de la terapia con MitraClip en pacientes que presentaban IM grado 3 o 4 y síntomas, o que tenían signos incipientes de compromiso de ventrículo izquierdo (FEVI <60%, diámetro telesistólico >45mm).

Los datos de los primeros 107 pacientes incluidos tanto en éste como en el EVEREST II (Endovascular Valve-Edge-to-Edge Repair Study II) mostraron una incidencia baja de eventos adversos en fase inicial, principalmente relacionada con sangrado (3.4%).

Además, se observó una alta tasa de éxito en el procedimiento, ya que en el 79% de los casos se logró una reducción del grado de IM menor o igual a 2 tras el implante. No se observó ninguna embolización, pero sí se registró el desprendimiento de uno de los velos en un 9% de los casos (59).

Fue este segundo estudio, el EVEREST II, el que asentó los criterios anatómicos “óptimos” para la reparación mitral mediante este dispositivo (54,67) (*Tabla 3*).

|                                        | Anatomía favorable                                                                                           | Anatomía menos favorable o desfavorable                                                                                                                                                                                                    |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Localización de la patología</b>    | Patología no comisural                                                                                       | Patología comisural, perforaciones o clefts.                                                                                                                                                                                               |
| <b>Calcificación</b>                   | Ausente o mínima                                                                                             | Calcificación moderada o severa del anillo o de la zona de captura de velos                                                                                                                                                                |
| <b>Gradiente medio transmitral</b>     | Gradiente transmitral <4mm Hg                                                                                | Estenosis mitral (gradiente medio >5mm Hg)                                                                                                                                                                                                 |
| <b>Área valvular mitral (AVM)</b>      | AVM >4 cm <sup>2</sup>                                                                                       | AVM <4 cm <sup>2</sup>                                                                                                                                                                                                                     |
| <b>Longitud de velo mitral</b>         | >10 mm                                                                                                       | <7 mm                                                                                                                                                                                                                                      |
| <b>Insuficiencia mitral primaria</b>   | Amplitud del flail <15mm<br>Altura del flail <10mm<br>Patología en 1 sólo segmento<br>Velos de grosor normal | Amplitud del flail >15mm<br>Altura del flail >10mm<br>Patología en multisegmento<br>Flail de elevada movilidad con rotura de cuerdas<br>Engrosamiento importante y difuso (5mm en diástole) y velos redundantes (E. Barlow)<br>DTSVI >55mm |
| <b>Insuficiencia mitral secundaria</b> | Profundidad de coaptación <11mm<br>Longitud de coaptación <sup>3</sup> 2mm                                   | DTSVI > 70mm                                                                                                                                                                                                                               |

**Tabla 3.** Criterios de reparación mitral borde-a-borde tras estudio EVEREST.

En él, un total de 279 pacientes se asignaron al azar en proporción 2:1 a recibir RPBB o tratamiento quirúrgico, ya sea por reemplazo o reparación mitral. El 73% de los casos correspondían a IMD y se excluyó a pacientes con FEVI menor a 25% o diámetro telediastólico de ventrículo izquierdo superior a 55mm. Los datos demostraron que, siguiendo unos criterios estrictos anatómicos, el 78% de los pacientes tratados con RPBB mantuvieron un grado de insuficiencia residual al año  $\leq 2$ , lo que se acompañó de una mejora sintomática significativa comparable a la obtenida tras el tratamiento quirúrgico (clase funcional NYHA  $\leq$  III en 2% de pacientes de grupo percutáneo vs 13% en grupo quirúrgico). Además, se observó cierto grado de remodelado ventricular con una disminución de volúmenes ventriculares, que fue similar en ambos grupos. La cohorte de pacientes que recibió tratamiento percutáneo presentó menos eventos peri-procedimiento (MACE de 15% vs 48% en el grupo quirúrgico) aunque esto se debió principalmente a la necesidad de transfusión sanguínea. A 5 años, los resultados en términos de mortalidad e IM residual fueron similares en ambos grupos (20.8% vs 26.8%,  $p=0.4$ ). Sin embargo, los datos arrojaron una tasa de reintervención mitral



mayor en el grupo tratado percutáneamente respecto al grupo tratado quirúrgicamente (20% vs 2%) lo que inicialmente planteó dudas sobre la durabilidad de la reparación. Posteriormente se demostró que la mayoría de las reintervenciones en el grupo de tratamiento percutáneo ocurrieron durante el primer año de seguimiento (78% dentro de los primeros seis meses) siendo menos comunes posteriormente y comparables a la necesidad de reintervención del grupo inicialmente tratado quirúrgicamente (55).

Dentro de esta serie de estudios se buscó también analizar los efectos de esta terapia en población de alto riesgo no tributarios a cirugía. El subestudio EVEREST High-Risk Registry incluyó a 78 pacientes con mortalidad quirúrgica estimada mayor o igual al 12% que fueron asignados al azar a recibir reparación percutánea o tratamiento médico (52). En este caso, la supervivencia fue mayor en el grupo reparado percutáneamente (76% vs 55%) y se redujo la tasa de recurrencia de insuficiencia cardíaca en este grupo (16% vs 42%). Estos resultados se confirmaron al combinar estos pacientes con los 273 del registro EVEREST REALISM (Real World Expanded Multicenter Study of the MitraClip System). En esta cohorte, a un año se redujo la IM a grado 2 o menor en el 84% de los pacientes y se mejoró la clase NYHA a I-II en 83% de los casos observando unas cifras de mortalidad del 22.8%. En pacientes con riesgo prohibitivo para la cirugía, la terapia con RPBB produjo resultados similares, mejorando de forma sustancial la calidad de vida y reduciendo el número de hospitalizaciones por insuficiencia cardíaca (68).

Registros más amplios en Europa, como el ACCESS-EU (the Amsterdam Center for Contemporary European Studies- A two-phase observational study of the MitraClip system in Europe)(69) que incluyó a 567 pacientes considerados de alto riesgo quirúrgico, en su mayoría con IM de causa funcional(69%), tratados en 14 centros europeos con RPBB, arrojaron resultados similares. La mortalidad peri-procedimiento

fue del 3.4%, y el éxito del implante del 99.6%, manteniendo a un año un grado de IM residual  $\leq 2$  en el 79% de los pacientes y una clase funcional NYHA  $\leq$ II en el 71%.

Otros registros europeos como el TCVT-EU (Transcatheter Valve Treatment Sentinel Pilot Registry in Europe) con más de 600 pacientes incluidos y el TRAMI (Transcatheter Mitral Valve Interventions) con más de 1000, mostraron un alto éxito del procedimiento con reducción de la IM en 95-96% de los casos (70,71). A los 12 meses, más del 70% de los pacientes del TCVT-EU y aproximadamente el 63.3% de los del TRAMI se encontraban en clase funcional NYHA I o II.

A pesar de estos estudios (*Tabla 4*), cabe destacar que hasta 2018 no se disponía de datos que compararan la efectividad de la RPBB con el tratamiento médico óptimo (TMO) en población con IMF.

|                                                  | EVEREST II-<br>REALISM | ACCESS EU | TRAMI | Sentinel |
|--------------------------------------------------|------------------------|-----------|-------|----------|
| Número pacientes                                 | 351                    | 567       | 1064  | 628      |
| IMF (%)                                          | 70.1                   | 69        | 71    | 72       |
| STS score (%)                                    | 5                      | -         | 6     | -        |
| Euroscore (%)                                    | -                      | 23        | -     | 20.4     |
| IM $\leq$ 2 post procedimiento (%)               | 86                     | 91        | 96    | 95       |
| Sangrado severo / transfusión (%)                | 13                     | 3.9       | 11.2  | 7        |
| Mortalidad hospitalaria (%)                      |                        | 2         | 2.9   | 2.4      |
| Mortalidad al año (%)                            | 22.8                   | 11.8      | 20.3  | 15.3     |
| IM $\leq$ 2 al año (%)                           | 84                     | 79        | -     | -        |
| NYHA $\leq$ 2 al año (%)                         | 83                     | 71        | 63.3  | 70       |
| Hospitalizaciones por insuficiencia cardíaca (%) | -                      | -         | 14.1  | 22.8     |

**Tabla 4.** Comparativa de los principales estudios previos a la publicación de COAPT /MITRA-FR en reparación percutánea borde a borde mitral

Fue ese año cuando, de manera paralela, se publicaron los controvertidos resultados de los estudios COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) (56) y MITRAFR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) (72). El primero incluyó a 614 pacientes, en su mayoría con IMF, una FEVI 25-50%, IM moderada o severa y que se encontraban en clase NYHA II-IV a pesar de recibir TMO. Fueron asignados al azar en una proporción 1:1 a recibir RPBB o TMO. A los 12 meses, el 74.3% en el grupo de RPBB versus el 55% en el grupo de TMO alcanzaron una clase funcional NYHA  $\leq 2$ . A los dos años, la cohorte tratada con RPBB experimentó menos hospitalizaciones por insuficiencia cardíaca (38.5% vs 67.9%,  $p < 0.001$ ) y menor mortalidad (29.1% vs 46.1%,  $p < 0.001$ ). Stone et al (73) publicaron recientemente los resultados de seguimiento a 5 años del estudio COAPT en los cuales la mejora en supervivencia y clase funcional, así como la reducción de la rehospitalizaciones, seguía siendo superior en el grupo tratado con RPBB. El grupo que inicialmente recibió sólo tratamiento médico tuvo una alta tasa de mortalidad en los primeros dos años. Tras estos dos años, casi el 45% de los supervivientes del grupo control recibió tratamiento con RPBB, lo que mejoró su pronóstico y redujo la tasa de hospitalización por insuficiencia cardíaca. Por otro lado, en el MITRAFR, que incluyó a 304 pacientes con IM principalmente funcional, FEVI 15-40%, fracción regurgitante  $\geq 30$  ml y que se encontraban en clase funcional NYHA II-IV aleatorizados 1:1 a RPBB vs TMO, no encontraron diferencias en mortalidad o rehospitalizaciones por insuficiencia cardíaca a 12 meses (63.8% vs 67.1% en RPBB vs TMO). Esta disparidad en los resultados de estos amplios estudios podría ser explicada en parte por las distintas características de los pacientes, tanto desde el punto de vista ecocardiográfico como clínico. El estudio COAPT incluyó a un

mayor porcentaje de pacientes con TMO ya iniciado, con una función ventricular más preservada, diámetros ventriculares más reducidos y sin disfunción ventricular derecha moderada-severa o hipertensión pulmonar severa. También podría haber influido la posible diferente experiencia de los operadores de los distintos ensayos dado el peor resultado ecocardiográfico post-procedimiento y en seguimiento en MITRAFR (IM grado 3 o 4 en 17 % vs 5% en COAPT) (74) (Tabla 5).

|                                | COAPT                                           | MITRAFR                                  |
|--------------------------------|-------------------------------------------------|------------------------------------------|
| <b>Inclusión</b>               |                                                 |                                          |
| IM moderada o severa           | EROA $\geq$ 30mm <sup>2</sup> y/o Vol Reg >45mL | EROA>20mm <sup>2</sup> y/o Vol Reg >30mL |
| DTSVI                          | $\leq$ 70mL                                     |                                          |
| FEVI (%)                       | 20-50                                           | 15-40                                    |
| PASP                           | <70mmHg                                         |                                          |
| TMO                            | Dosis máximas toleradas                         | Variable, con ajuste durante el estudio  |
| <b>Características basales</b> |                                                 |                                          |
| EROA<30mm <sup>2</sup> (%)     | 14                                              | 52                                       |
| EROA 30-39 (%)                 | 46                                              | 32                                       |
| EROA $\geq$ 40                 | 41                                              | 16                                       |
| VTDVI (mL/m <sup>2</sup> )     | 101+/-34                                        | 135+/-35                                 |

**Tabla 5.** Diferencias principales en la inclusión y características basales de los pacientes de los estudios COAPT y MITRAFR. DTSVI, diámetro telesistólico de ventrículo izquierdo; PASP, presión arterial sistólica pulmonar; VTDVI, volumen telediastólico de ventrículo izquierdo.

A raíz de estos resultados, Grayburn et al (75) sugirieron dos perfiles distintos de IM: la IM “proporcionada” o aquella en la que el volumen regurgitante está relacionado con la dilatación ventricular y la “desproporcionada” o aquella en la que el volumen regurgitante no parece estar en consonancia con el grado de dilatación ventricular. Los pacientes incluidos en el MITRA-FR presentaban en su mayoría “IM proporcionada” lo

que sugiere que podrían beneficiarse más de estrategias dirigidas a reducir la disfunción ventricular. Por el contrario, en el estudio COAPT, los pacientes presentaban en su mayoría ventrículos de dimensiones más reducidas que en MITRA-FR y con mayor volumen de regurgitación mitral, lo que les podría hacer más susceptibles a responder mejor a la RPBB. Esta hipótesis se ha confirmado en los registros EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) (76) y GIOTTO (Italian Society of Interventional Cardiology GISE Registry of Transcatheter Treatment of Mitral Valve Regurgitation Registry) (77) donde los pacientes con criterios COAPT o con “IM desproporcionada” presentaban, tras la RPBB, menores tasas de mortalidad mientras que aquellos con perfil tipo MITRAFR no obtenían tanto beneficio.

En los estudios comentados, la RPBB ha demostrado ser un procedimiento relativamente seguro y con tasas bajas de complicaciones siendo la mayoría de ellas relacionadas con sangrado del acceso vascular (33). Sin embargo, es importante destacar que, aunque menos frecuente, existen otras complicaciones como la perforación o desgarró de velo o el *missmatch* o falta de adaptación de postcarga que pueden ser potencialmente fatales (78).

### 1.2.3. Selección de pacientes

Actualmente las guías de actuación clínica de la Sociedad Europea de Cardiología recomiendan con nivel IIb y grado de evidencia B la reparación mitral percutánea borde-a-borde en pacientes con IMD y alto riesgo quirúrgico en los que dicho procedimiento sea factible y considerado no fútil mientras que, en pacientes en que la insuficiencia mitral sea funcional, la recomendación asciende a grado IIa nivel de

evidencia B para pacientes “seleccionados” con alto riesgo quirúrgico (16) todo ello tras evaluación rigurosa por equipo multidisciplinar.

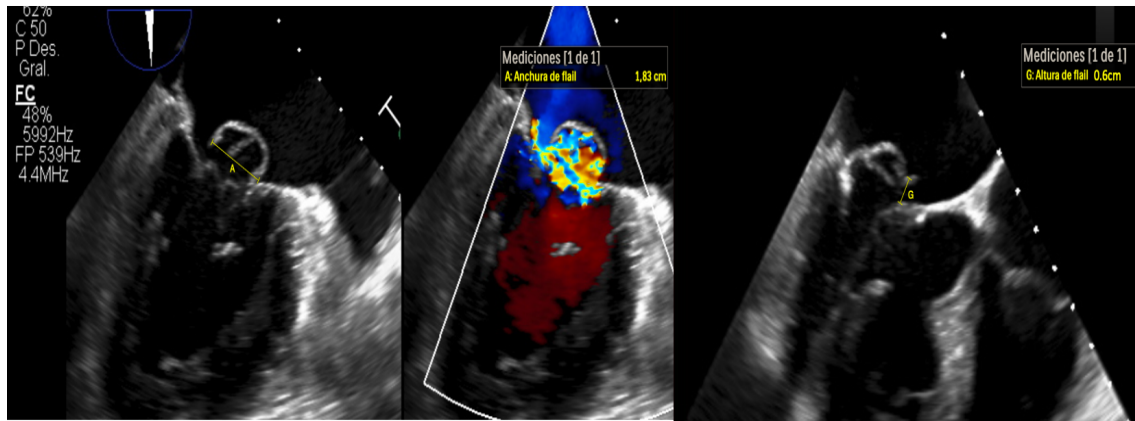
### *Selección anatómica*

La viabilidad técnica del procedimiento depende de la selección de una anatomía óptima, la cual se determina mediante un análisis ecocardiográfico. Los criterios clásicamente considerados como idóneos para la RPBB se extrapolaron, como previamente comentado, del estudio EVEREST I y II, si bien las guías actuales se rigen por los criterios COAPT en casos de IMF.

En los últimos años, no obstante, se ha ido expandiendo su uso en válvulas anatómicamente más complejas a medida que se ha ido ganando experiencia con la técnica, y con la mejora de los dispositivos (79,80).

En el registro EXPAND (80), que consideró como criterios de mayor complejidad anatómica la presencia un gap de coaptación ancho ( $\geq 15\text{mm}$ ), flail  $\geq 10\text{mm}$ , jets comisurales, área valvular mitral disminuida, una zona de aterrizaje calcificada y un tejido valvular mínimo, los pacientes con al menos una de estas características fueron más propensos a presentar algún grado de insuficiencia mitral residual. Sin embargo, a los 30 días seguía habiendo una tasa de reducción de IM a grado  $\leq 2$  del 96.9% a pesar de dicha complejidad anatómica.

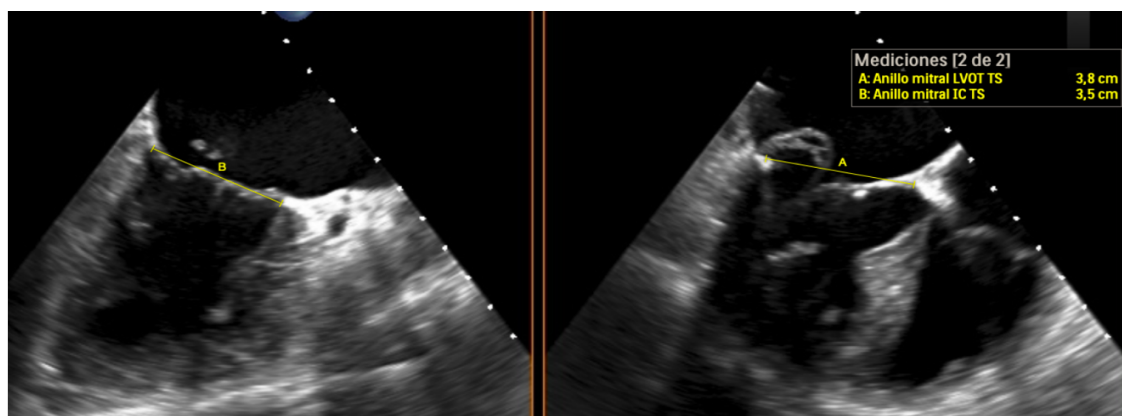
Varios estudios han respaldado estos resultados observando mayor riesgo de reintervención o reaparición de IM severa en presencia de *flail* y gap de coaptación anchos (81) o restricción de velo posterior (82) (*Figura 11*).



**Figura 11.** Ejemplo de *flail* amplio que condiciona una insuficiencia mitral severa

Asimismo, Itabashi et al comprobaron cómo el AVM basal  $\leq 3.8\text{mmHg}$  era el mejor parámetro para predecir un gradiente transmitral postprocedimiento  $\leq 4\text{mmHg}$  (83), de nuevo en línea con lo publicado por los grupos EVEREST y COAPT.

Además existen otros factores de análisis más complejo y, por tanto, no usado en la práctica habitual, como el índice velo-anillo (84), la presencia de *tenting* asimétrico (85), la reserva de coaptación (86) o el diámetro anteroposterior  $\geq 35\text{mm}$  (87), que han resultado predictores de resultado en cuanto a insuficiencia mitral residual post RPBB (Figura 12).



**Figura 12.** Medida ecocardiográfica de los diámetros del anillo mitral (distancia anteroposterior (A) e intercomisural (B) y anteroposterior (A))

Cabe destacar que se ha de tener en cuenta no sólo la selección anatómica sino la experiencia del equipo operador al valorar la viabilidad de esta terapia (88,89).

### *Selección clínica*

Además de la selección de candidatos técnicamente óptimos, el equipo multidisciplinario debe evaluar cuidadosamente las comorbilidades y datos clínicos que puedan ensombrecer el pronóstico vital de estos pacientes. Por ejemplo, el registro GRASP-IT (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation in Italy) (90) ya observó, en los primeros años de la terapia, mayores tasas de mortalidad de cualquier causa o insuficiencia cardíaca en pacientes con FEVI <30%, IMF isquémica, enfermedad renal, enfermedad obstructiva crónica (EPOC) y la presencia de ingresos por insuficiencia cardíaca previos a la intervención.

En cuanto a la IMF isquémica, que por sí sola ya está asociada a un peor pronóstico (91,92), cabe destacar que los datos del estudio COAPT arrojan una mayor supervivencia de estos pacientes tras RPBB en comparación con aquellos tratados sólo médicamente (56). Además, otros estudios como el de Kitamura et al (93) observaron un beneficio similar de la terapia tanto en pacientes isquémicos como en no isquémicos. Otros factores clínicos que han demostrado estar asociados con una mayor mortalidad son la presencia de valvulopatía aórtica intervenida, la fibrilación auricular (FA), la EPOC (86), la enfermedad renal, la hipertensión pulmonar (HTAP) (87,88), la disfunción ventricular derecha o la presencia de IT.

Boerlange-vanDijk et al (94) observaron que, de los 84 pacientes tratados con RPBB de su estudio, aquellos con cirugía aórtica previa presentaron mayor mortalidad a dos años



(HR: 4.5; 95% CI:1.7-12.2,  $p= 0.003$ ) algo que ya objetivó también el ya comentado TRAMI (95) con similares resultados a 1 año (HR:2.12;95% CI: 1.32-3.41,  $p= 0.002$ ). Por otro lado, Godino et al mostraron cómo, en una cohorte de 314 pacientes tratados con RPBB, la presencia de FA, FEVI <25% y ProBNP elevado eran predictores de mortalidad cardíaca a 2 años (96).

Además, la enfermedad renal crónica y la FA, que clásicamente se han mostrado en numerosos escenarios como predictores independiente de mortalidad, también han resultado predictores de pronóstico en los pacientes tratados con RPBB tanto en registros como el TRAMI o el GRASP previamente mencionados.

En cuanto a la disfunción ventricular derecha, varios parámetros como el TAPSE (97,98) u otros factores como la velocidad sistólica pico en Doppler tisular <9.5cm/s (99) han mostrado ser predictores de mortalidad en seguimiento en esta población. Del mismo modo, la presencia de insuficiencia tricuspídea, que a menudo coexiste con la IM, puede asociarse con un peor pronóstico. En el registro TRAMI, su presencia estuvo asociada con mortalidad a un año (HR: 2.01; 95%CI: 1.3-3.3,  $p= 0.004$ ) (100) hallazgo que se replicó en el registro GRASP IT (101)y en el estudio aleatorizado COAPT (102).

En cuanto al estado físico del paciente, también se conoce que puede ser predictor de rehospitalización a pesar de tratamiento médico óptimo o MTEER. En un subanálisis del estudio COAPT, el estado físico evaluado mediante el Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS) y la capacidad de ejercicio por el 6-minute walk distance (6MWD) resultó ser predictor de rehospitalización y mortalidad en ambas cohortes (103). En este sentido, la clase funcional NYHA también ha resultado ser predictora de mortalidad en varios estudios previos en los que el presentar una clase funcional avanzada (NYHA IV) fue predictor de mortalidad a un año (90,92,103).

### *Poblaciones especiales*

La RPBB se ha evaluado con especial énfasis en presencia de disfunción ventricular entendida como FEVI deprimida. El subanálisis del estudio COAPT se logró una reducción de la tasa de mortalidad a 2 años en pacientes tratados con RPBB tanto en aquellos con FEVI >40% (HR 0.5; 95% CI:0.39-0.65) como en aquellos con FEVI ≤40% (HR 0.60; 95% CI:0.35-1.05) mejorando asimismo la calidad de vida y disminuyendo el grado de IM a 2 años de seguimiento (104).

Otros grupos han valorado esta terapia en FEVI severamente deprimida obteniendo buenos resultados peri procedimiento y sin observar diferencias en función de FEVI en cuanto a mortalidad y mejora de clase funcional (56,105–108). Sin embargo, los pacientes con FEVI deprimida presentaban tasas más altas de reingresos por insuficiencia cardíaca (56) y, en casos de disfunción muy severa, mayores eventos cardiovasculares (109). Sin embargo, es importante señalar que Godino et al obtuvieron resultados contradictorios, al observar en su población mayor mortalidad cardíaca en la cohorte con FEVI ≤25% (96).

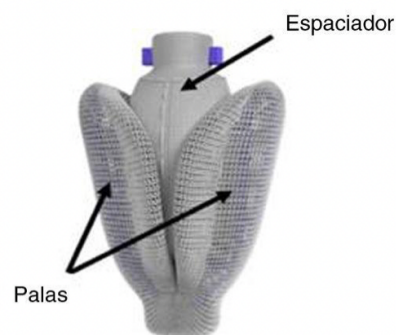
Como se mencionó previamente, principalmente a raíz de los resultados de los estudios COAPT y MITRAFR, se ha prestado especial interés en la valoración de la función ventricular y su relación con el grado de IM. Para ello, uno de los parámetros evaluados es el tamaño ventricular, ya sea por dimensiones volumétricas o de diámetros de cavidad. En el registro GRASP-IT, se encontró que un ventrículo dilatado (VTSVI >110ml) era predictor de mortalidad y rehospitalización por insuficiencia cardíaca (HR: 1.86;95% CI:1.2-3.0; p<0.01) (90) y en el estudio de Godino et al (96), un VTDVI >216ml fue considerado predictor de mortalidad cardíaca a 2 años (HR:2.631;95% CI: 1.06-6.50, p=0.036). Otro parámetro utilizado a partir de los

estudios mencionados es el área de orificio de regurgitación (EROA), que también ha demostrado ser predictor de mayor grado de IM y mortalidad en seguimiento (110).

#### 1.2.4. Otras terapias percutáneas

##### *Pascal*

El dispositivo de reparación mitral borde a borde Pascal (Edwards Lifesciences, Irvine, CA, Estados Unidos) también replica el procedimiento quirúrgico de Alfieri, aunque presenta algunas diferencias respecto al dispositivo MitraClip. Está fabricado principalmente con nitinol, tiene palas más anchas y convexas y cuenta con un espaciador central de 10mm diseñado para ocupar el orificio regurgitante residual lo que permite además incrementar la superficie de coaptación disminuyendo la tensión sobre los velos. También tiene la capacidad de elongación para navegación en espacio subvalvular y la posibilidad de captura individual de los velos en anatomías complejas (111) (*Figura 13*).



**Figura 13.** Dispositivo Pascal en posición cerrada mostrando el espaciador central y las palas anchas y gruesas.

El primer uso del dispositivo Pascal data de 2016, cuando se utilizó en una cohorte de 23 pacientes con IM grado 3 o 4 con alto riesgo quirúrgico. En ese estudio, se observó una alta eficacia técnica, con un éxito en el 96% de los casos, y un bajo porcentaje de eventos adversos peri procedimiento, con solo un paciente experimentando un sangrado menor y otro, un accidente cerebrovascular transitorio (112).

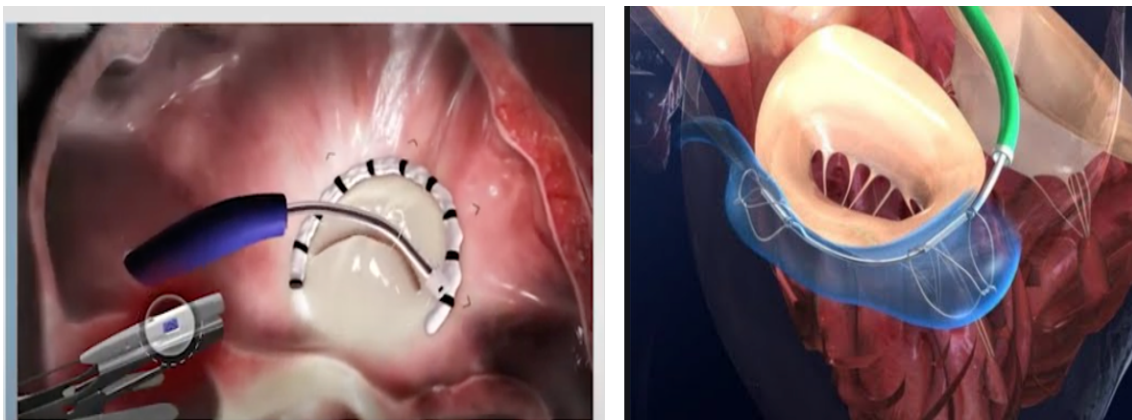
Hasta la fecha, se han recopilado datos a dos años del estudio CLASP (Edwards PASCAL Transcatheter Mitral Valve Repair System Study). En este estudio, 124 pacientes con IM grado 3 o 4 sintomática con alto riesgo quirúrgico fueron reparados percutáneamente con el dispositivo PASCAL (113). Los datos obtenidos muestran una baja tasa de eventos adversos peri procedimiento, con un evento compuesto en un 8.1% de los casos, principalmente debido a sangrado. La supervivencia a dos años alcanzó el 80% y hubo una baja tasa de rehospitalizaciones que afectó al 22% de los pacientes. Durante ese periodo, se logró un grado de IM menor a 2 en el 97% de los casos, y hasta el 93% de los pacientes experimentaron una mejora en su clase funcional a NYHA inferior o igual a II.

El estudio CLASP IID/IIF actualmente en curso aleatorizará a 1275 pacientes con IM de etiología funcional y degenerativa a tratamiento con RPBB con los dispositivos MitraClip o Pascal. Los datos preliminares de la cohorte degenerativa han mostrado la no-inferioridad de este dispositivo en términos de seguridad del procedimiento y durabilidad de la reparación (114). Además, otros grupos han realizado comparaciones retrospectivas entre los dispositivos MitraClip y Pascal, sin objetivar diferencias en cuanto al grado residual de IM o la clase funcional NYHA en el seguimiento (115). En la actualidad, el mercado cuenta con la segunda generación de este sistema (Pascal Precision) que busca ofrecer una mayor estabilidad y maniobrabilidad del catéter guía.

Asimismo, se dispone de dos tamaños diferentes: el Pascal P10, con palas de 10mm de grosor y el Pascal Ace con palas de 6mm de grosor.

#### *Dispositivos para anuloplastia directa o indirecta*

De manera similar a la anuloplastia quirúrgica, la anuloplastia percutánea persigue reducir la circunferencia del anillo mitral y atraer el velo posterior y facilitar así la coaptación de las valvas. Esto se puede conseguir de forma directa, o indirecta a través del seno coronario. Existen varios dispositivos de anuloplastia a día de hoy siendo los más usados en nuestro entorno el Cardioband para anuloplastia directa y el Carrillon para anuloplastia indirecta (*Figura 14*).



**Figura 14.** A la izquierda, dispositivo de anuloplastia directa Cardioband. A la derecha, dispositivo de anuloplastia indirecta Carrillon

El sistema Cardioband (ValtechCardio, Inc., Or Yehuda, Israel) obtuvo el marcado CE en 2015 para el tratamiento de la IMF. Se implanta bajo anestesia general y guiado por ecocardiografía transesofágica. A través de un acceso venoso femoral de 25 french, y tras obtener el acceso transeptal, se avanza el sistema de implante de la banda de dacrón que se posiciona de comisura a comisura fijándolo con 12-17 fijadores o anclas de acero

inoxidable de 6mm en función del tamaño elegido. Durante el procedimiento, se presta especial atención a la localización de la arteria circunfleja (116).

El dispositivo se evaluó inicialmente en pacientes con IMF y FEVI  $\geq 25\%$  en un registro prospectivo de factibilidad (117). Los resultados mostraron una tasa de éxito de implante del 100%, con una reducción significativa del diámetro septolateral en el 93.6% de los pacientes. La tasa de mortalidad intrahospitalaria fue de 6.5% y el 29% de los pacientes experimentó algún tipo de efecto adverso mayor a los 30 días. La IM se redujo de forma significativa a grado igual o menor a 2 en el 86% de los pacientes a 6 meses, y el 81% de ellos presentaba una clase funcional NYHA I-II en ese momento.

Por otro lado, el sistema Carillon Mitral Contour System (Cardiac Dimensions Inc., Kirkland, WA) se posiciona a través de un acceso yugular derecho en el seno coronario para su posterior cinchado. Este sistema se ha evaluado en pacientes con IMF y FEVI  $< 40\%$  en los estudios TITAN y TITAN II (118,119). Las tasas de éxito de implante oscilaron entre el 68% y el 83%, con tasas de efectos adversos mayores a los 30 días que variaron entre el 1.9% y el 2.8%. En ambos estudios, se observó una reducción significativa de la IM, así como una mejoría significativa en la clase funcional. Posteriormente, el estudio REDUCE-FMR (120) aleatorizó 120 pacientes a recibir el dispositivo Carillon o tratamiento médico. En el grupo tratado con el dispositivo, el 50% de los pacientes experimentó una mejora significativa de la IM, el 26% no se modificó y el 24% empeoró.

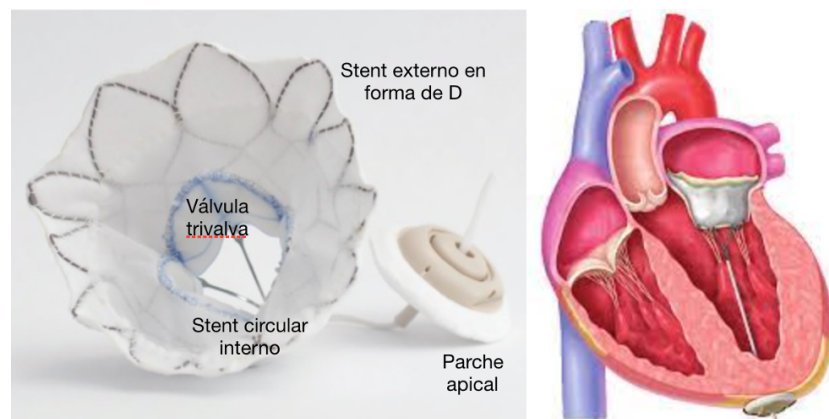
#### *Reparación transcatéter mediante neocuerdas*

Para el tratamiento de IMD por prolapso o flail se han desarrollado recientemente dos sistemas de reparación transapical mediante Neocuerdas: el sistema de liberación artificial de cuerdas NeoChord (NeoChord, Inc., MN, USA) y el sistema de reparación

valvular mitral en corazón latente Harpoon (Edwards LifeSciences, CA, USA). Ambos han mostrado en estudios iniciales ser eficaces en la reducción del grado de IM y clase funcional NYHA a un año en la mayoría de los pacientes (121,122).

#### *Implante transcatóter de prótesis mitral*

Actualmente, existen varias prótesis dedicadas para su implante en anatomías mitrales nativas tales como la válvula Intrepid (Medtronic), Cardiovalve (Valtech Cardio Ltd., Or Yehuda, Israel) o la válvula Tendyne (Abbott). En nuestro medio, la más usada es la válvula Tendyne, de liberación transapical, que consta de una válvula trivalva de pericardio porcino montada sobre un stent externo en forma de D. Es autoexpandible y cuenta con un sistema de fijación ajustable al ápex (*Figura 15*).



**Figura 15.** Prótesis valvular mitral Tendyne.

El primer estudio publicado sobre esta prótesis incluyó a 100 pacientes, y los resultados mostraron un éxito técnico del 96%, una tasa de mortalidad a los 30 días del 6% y una tasa de mortalidad al año del 26%. En los supervivientes a un año, se observó que el 88.5% se encontraban en clase funcional NYHA  $\leq$ II (123).

Además, también se ha explorado la posibilidad de realizar el implante transcáteter de prótesis mitral empleando prótesis originalmente diseñadas para el implante percutáneo aórtico. Esto se ha aplicado principalmente en pacientes con degeneración de bioprótesis, anuloplastia previa o calcificación severa del anillo (procedimientos “valve-in-valve”, “valve-in-ring” o “valve-in-MAC”). Sin embargo, los resultados a corto y medio plazo de estos procedimientos han sido modestos, especialmente en casos de “valve-in-MAC” (124).

El reemplazo valvular percutáneo de la válvula mitral se encuentra en fase aún inicial de desarrollo y presenta desafíos importantes que deben superarse. El primero, es el posible riesgo de obstrucción del tracto de salida de ventrículo izquierdo al movilizar el velo anterior hacia el septo interventricular. Para abordar este problema, se están utilizando y desarrollando varias estrategias en la actualidad, como la ablación septal y el LAMPOON (laceration of the anterior mitral leaflet to prevent outflow obstruction) (125). El segundo aspecto a considerar es el tamaño valvular mitral, que a menudo está dilatada en pacientes con enfermedad mitral avanzada y puede requerir prótesis de mayor tamaño y dispositivos de entrega adecuados. Además, en el caso de válvulas mitrales nativas no calcificadas, se necesitarán mecanismos adicionales para asegurar la estabilidad y el sellado de la prótesis sin dañar estructuras adyacentes. Por último, la durabilidad a largo plazo de las prótesis y la necesidad de anticoagulación son aspectos que aún no se comprenden completamente en este contexto.

#### 1.2.5. Justificación del estudio

La reparación percutánea borde-a-borde (RPBB) de la válvula mitral se ha convertido en la terapia transcáteter más utilizada para el tratamiento de la IM (33). No obstante, la



mayoría de estudios previos a esta tesis excluyeron a poblaciones de alto riesgo, como pacientes con disfunción ventricular izquierda severa o con anatomía valvular clásicamente considerada “compleja”. Además, la reciente discrepancia en los resultados publicados de los estudios aleatorizados MITRAFR y COAPT subraya la necesidad de estudiar y caracterizar aún más a los candidatos a RBPP mitral para optimizar la selección de pacientes, la técnica y el momento de intervención adecuados. Una población que ha sido ampliamente excluida en los estudios y registros de RPBB es la que corresponde a aquellos pacientes con calcificación del anillo mitral (MAC). Esto se debe probablemente a la asunción de que la calcificación podía extenderse a velos y zona de captura de los dispositivos, así como al riesgo potencial de estenosis valvular residual. Sin embargo, la calcificación del anillo mitral es una condición con alta prevalencia (hasta el 30% de pacientes con IM) (126,127) y con una mayor comorbilidad (128–131) y sobre la que la experiencia en el campo quirúrgico es pobre, con tratamientos que requieren una mayor complejidad y que están asociados a peores resultados (132–139). Por lo tanto, es de especial interés investigar una terapia alternativa menos invasiva que pueda resultar segura y eficaz en este escenario como podría ser la RPBB.

Otro grupo de pacientes que genera controversia en cuanto a la indicación de tratamiento mediante RPBB es el que corresponde a aquellos pacientes con FEVI deprimida (<40%) especialmente después de los resultados de los estudios MITRAFR y COAPT. Se ha planteado la hipótesis de que podría existir un “punto de no retorno” en el que, a pesar de ser técnicamente factible, la RPBB no añada beneficio clínico (75). De este modo, contar con métodos de caracterización de la función y estado ventricular más precisos, reproducibles y menos afectados por condiciones de precarga y postcarga que la FEVI o tamaños ventriculares, como puede ser la determinación del strain global

longitudinal de ventrículo izquierdo, podría ayudar en la selección de candidatos y momento de intervención adecuados (140–142). Estas consideraciones motivaron la segunda parte de esta tesis, en la que se valoró el valor pronóstico del análisis basal del strain global de ventrículo izquierdo en pacientes con FEVI <40% que fueron tratados con RPBB.

## **2. HIPÓTESIS**



En pacientes con calcificación del anillo mitral y/o disfunción ventricular, la reparación mitral transcatheter tiene el potencial de disminuir la insuficiencia mitral y mejorar los síntomas asociados, la calidad de vida de los pacientes y la tasa de rehospitalizaciones debido a insuficiencia cardíaca.



### **3. OBJETIVOS**





## Objetivo principal

1. Determinar la seguridad y eficacia de la RPBB en poblaciones de alto riesgo anatómico y clínico, centrándose específicamente en pacientes con calcificación del anillo mitral y en aquellos con FEVI deprimida.

## Objetivos secundarios

1. Identificar las variables anatómicas y clínicas asociadas a un peor resultado de la RPBB a largo plazo en términos de reintervención, grado de IM residual o clase funcional.
2. Analizar el valor pronóstico del strain global longitudinal de ventrículo izquierdo en términos de mortalidad cardiovascular tras la RPBB.



## **4. COMPENDIO DE PUBLICACIONES**



#### 4.1. Artículo 1

Transcatheter edge-to-edge mitral valve repair in patients with mitral annulus calcification

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# Transcatheter edge-to-edge mitral valve repair in patients with mitral annulus calcification

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## KEYWORDS

- chronic heart failure
- mitral regurgitation
- mitral valve repair

## Abstract

**Background:** MAC is commonly found in patients affected with MR, and it is associated with high morbidity, mortality and worse cardiac surgical outcomes. Transcatheter edge-to-edge repair could be an alternative treatment, although there is little evidence in this population.

**Aims:** The aim of this study was to analyse the safety, efficacy and durability of MitraClip implantation in patients affected with mitral regurgitation (MR) and mitral annulus calcification (MAC).

**Methods:** We analysed the outcomes of 61 suitable patients affected with severe MR and moderate or severe MAC (the “MAC” group) and 791 patients with no or mild MAC (the “NoMAC” group) treated with the MitraClip device.

**Results:** Procedural success was similar (91.8% vs 95.1%,  $p=0.268$ , in MAC and NoMAC, respectively), with a very low rate of complications. At one-year follow-up, 90.6% of MAC and 79.5% of NoMAC patients had MR grade  $\leq 2$  ( $p=0.129$ ), 80% in both groups remained in NYHA Functional Class  $\leq \text{II}$ , and a significant reduction in cardiac readmissions was observed (65% vs 78% in MAC vs NoMAC,  $p=0.145$ ). One-year mortality tended to be higher in MAC patients (19.7% vs 11.3%,  $p=0.050$ ), with no difference in cardiovascular mortality (15.3% vs 9.2%,  $p=0.129$ ).

**Conclusions:** MitraClip use in selected patients with moderate or severe MAC is safe, feasible and achieves good clinical and echocardiographic results at one-year follow-up.

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## Abbreviations

|              |                                         |
|--------------|-----------------------------------------|
| <b>EDLVD</b> | end-diastolic left ventricular diameter |
| <b>EROA</b>  | effective regurgitant orifice area      |
| <b>ESLVD</b> | end-systolic left ventricular diameter  |
| <b>LVEF</b>  | left ventricular ejection fraction      |
| <b>MAC</b>   | mitral annular calcification            |
| <b>MR</b>    | mitral regurgitation                    |
| <b>NYHA</b>  | New York Heart Association              |
| <b>PCI</b>   | percutaneous coronary intervention      |
| <b>SPAP</b>  | systolic pulmonary artery pressure      |
| <b>TEE</b>   | transoesophageal echocardiography       |
| <b>TTE</b>   | transthoracic echocardiography          |

## Introduction

Mitral annular calcification (MAC) is a chronic degenerative process of increasing prevalence in developed countries which can be present in up to 24% of patients referred for mitral valve surgery<sup>1-3</sup>. It has been associated with several conditions including age and female sex, and some cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidaemia and smoking habit or chronic kidney disease. However, the mechanisms in which these conditions could lead to the development of MAC are still not clear. Clinically, MAC has been related to the presence of vascular disease, arrhythmia and mitral valve disease<sup>1,2,4-8</sup>.

Anatomically, MAC is found most commonly in the posterior annulus, but calcification might extend beyond the annulus<sup>1,9</sup> to the leaflets and subvalvular apparatus. Surgery of the mitral valve in this setting remains a challenge, MAC being a strong predictor of mortality and worse cardiac surgical outcomes in previous surgical reports<sup>1,10-18</sup>. In recent years, surgical techniques have evolved in this field accomplishing better survival rates; however, there remains a non-negligible rate of post-operative complications<sup>16,19</sup>. The high morbidity of patients with MAC together with the surgical complexity have fuelled an urgent need for less invasive strategies for treating these patients.

Transcatheter edge-to-edge mitral valve repair with the MitraClip system (Abbott Vascular) has been established as a valid alternative to surgery in high surgical risk patients with severe mitral regurgitation (MR)<sup>20-26</sup>. However, its efficacy in patients affected with MAC remains uncertain, given the paucity of data and the poor outcomes observed with the Alfieri surgical technique in this setting<sup>27-29</sup>. Moreover, these patients have been excluded from randomised clinical trials, based on the assumption that this calcification might extend to the leaflets or might induce high mitral gradients after edge-to-edge repair. Hence, we sought to analyse the safety and efficacy of the MitraClip system in patients who presented moderate or severe MAC and who were otherwise suitable candidates for this treatment, focusing on procedural success, durability and clinical benefit in a “real-world” setting.

## Methods

The Spanish MitraClip multicentre registry prospectively included all consecutive patients with symptomatic MR grade ≥3

undergoing transcatheter mitral valve repair from June 2012 in 24 participating institutions. This study evaluated the data from all patients enrolled by seven of these participating institutions. All patients signed informed consent for the procedure and all studies were performed with the approval of the local ethics committee.

In all participant sites, patients were evaluated by a multidisciplinary team, which included a non-interventional cardiologist, an interventional cardiologist, a cardiothoracic surgeon and an anaesthetist. All patients deemed to be at high risk for surgery were considered for percutaneous repair. Anatomically, patients with calcification that extended to the margin of the leaflets, had short (<7 mm) or thick leaflets (>5 mm) or had a preprocedural mean gradient greater than 5 mmHg or a mitral area <4 cm<sup>2</sup> were declined for percutaneous repair.

## BASELINE DEMOGRAPHICS AND ECHOCARDIOGRAPHIC PARAMETERS

Baseline demographic parameters included age, gender, weight and height, hypertension, diabetes mellitus, renal impairment and chronic haemodialysis, smoking, atrial fibrillation, previous cerebrovascular disease, ischaemic heart disease, New York Heart Association (NYHA) Functional Class, Society of Thoracic Surgeons (STS) score and heart failure hospitalisation during the previous year. Baseline echocardiographic parameters were based on preprocedural transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) following the European Association of Cardiovascular Imaging recommendations<sup>30,31</sup>. A categorical classification of MAC grade based on preprocedural echocardiography was used considering: 1) mild calcification of the annulus, when calcification was limited to less than one third of the annulus; 2) moderate calcification, when it involved one third to two thirds of the annulus, and 3) severe calcification, when it involved more than two thirds of the annulus or in case of a thickness >4 mm<sup>7,9</sup>. Two groups were defined according to the MAC grade: “NoMAC”, when no or mild annulus calcification was present, and “MAC”, when moderate or severe mitral annulus calcification was found.

## PROCEDURAL SUCCESS AND COMPLEXITY

Technical success was defined as correct implantation of at least one clip and the absence of procedural mortality or emergent cardiovascular intervention related to the implantation of the device or vascular access<sup>32</sup>. Procedural success was defined as MR grade reduction to 2 or less<sup>32</sup>. Procedure duration, number of clips and acute complications were recorded in order to assess the complexity of the repair. Procedure duration was defined as the duration from anaesthetic induction to the end of the procedure. Procedure-related bleeding and its severity were defined according to the Bleeding Academic Research Consortium (BARC) criteria<sup>32</sup>.

## ECHOCARDIOGRAPHIC AND CLINICAL FOLLOW-UP

At follow-up, NYHA Class, MR grade, mean mitral gradient, systolic pulmonary artery pressure (SPAP), left ventricular ejection



fraction (LVEF) and left ventricular dimensions were recorded as well as the need for subsequent mitral valve surgery, heart failure rehospitalisation and mortality.

## STATISTICAL ANALYSIS

Frequencies were calculated for categorical variables whereas mean±standard deviation (SD) or median (interquartile range) were calculated for numerical variables according to their distribution. Assessment of normality was performed using the Shapiro-Wilk test. Differences between groups were tested using the chi-square test for categorical variables and the Student's t-test, Kruskal-Wallis or Mann-Whitney U test for continuous variables. A 95% level of significance was applied in the statistical tests ( $p<0.05$ ). The Kaplan-Meier survival estimator was used to determine the time to all-cause mortality, cardiovascular mortality and readmissions for heart failure at one-year follow-up. Data from the survival curves and event-free survival rates along with the log-rank test were used for comparison between groups. Multivariate analysis of the association of MAC grade was performed using Cox proportional hazards modelling. The Stata 13.1 statistical package was used for data analysis (StataCorp).

## Results

### BASELINE DEMOGRAPHICS AND ECHOCARDIOGRAPHIC PARAMETERS

The baseline characteristics of the two groups are shown in **Table 1**. A total of 852 patients were included. Of these, 256 (30%) presented some degree of MAC: 42 (5.5%) were found to have moderate MAC and 19 (2.5%) had severe MAC. Therefore, 61 patients were allocated to the MAC group and 791 to the NoMAC group. MAC patients were older ( $78.3\pm 8.7$  vs  $72.8\pm 10.4$  years old,  $p=0.001$ ) and mostly female (44.3% male in the MAC group vs 66% male in the NoMAC group,  $p=0.001$ ), more frequently had a history of previous non-mitral valvular intervention (24.6% vs 11.3%,  $p=0.002$ ) and presented worse NYHA Functional Class (95% vs 85% NYHA Class  $\geq 3$ ,  $p=0.037$ ) and STS score (4 vs 3,  $p=0.027$ ) at the time of repair. On the other hand, NoMAC patients were more commonly smokers (48.5% vs 29.5%,  $p=0.004$ ). There were no differences between groups in relation to hypertension, diabetes mellitus, chronic kidney disease or haemodialysis, previous stroke, ischaemic heart disease, rate of previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) as well as for the EuroSCORE II.

Echocardiographic analysis showed that MAC patients had smaller left ventricular diameters (end-diastolic left ventricular diameter [EDLVD]  $53.1\pm 8.9$  vs  $60.8\pm 10.2$  mm,  $p<0.001$  and end-systolic left ventricular diameter [ESLVD]  $34.9\pm 10.6$  vs  $44.9\pm 13.4$  mm,  $p<0.001$ ) and better LVEF ( $52.5\pm 12.3$  vs  $40.4\pm 15\%$ ,  $p<0.001$ ). The mechanisms of MR were equally distributed between the groups (primary in 39.3% vs 30.1%, secondary in 41% vs 55%, and mixed in 19.7% vs 15.3% in the MAC and NoMAC groups, respectively). Most of the patients (90.2% of MAC patients and 85.7% of NoMAC patients) presented MR

grade 4 at the time of repair, although the MAC group exhibited larger effective regurgitant orifice areas (EROAs) ( $0.7\pm 0.3$  vs  $0.5\pm 0.3$  cm<sup>2</sup>,  $p=0.002$ ). MAC was mostly localised in the posterior annulus (77% of the patients) and, as expected, MAC patients had more challenging anatomies as they presented with greater sub-valvular apparatus calcification (35.6% vs 4.9%,  $p<0.001$ ), more eccentric jets (54.1% vs 31.3%,  $p<0.001$ ), and higher baseline transvalvular gradients ( $2.3\pm 1$  vs  $1.7\pm 0.8$  mmHg,  $p<0.001$ ), compared to NoMAC patients.

### PROCEDURAL OUTCOMES AND COMPLEXITY

Procedural data are shown in **Table 2**. Procedural success was similar in both groups (technical success: 95.1% vs 98.1%,  $p=0.144$ ; procedural success: 91.8% vs 95.1%,  $p=0.268$ , in the MAC and NoMAC groups, respectively) without differences in procedural duration ( $144\pm 61$  vs  $135\pm 66$  min,  $p=0.327$ , MAC vs NoMAC, respectively). Residual gradient was higher in MAC patients (3.0 vs 3.6 mmHg,  $p=0.001$ ) being greater than 5 mmHg in 18.5% of them, in comparison to 5% of NoMAC patients,  $p=0.001$  (**Figure 1A**).

Procedural complications were infrequent and occurred in 4 MAC patients and 70 NoMAC patients, mostly vascular access bleeding ( $p=0.549$ ). Conversion to surgery during index hospitalisation occurred in 2 patients (3.28%) in the MAC group and 5 patients (0.63%) in the NoMAC group ( $p=0.027$ ). Seven in-hospital deaths were reported, 1 in the MAC group, the others in the NoMAC group ( $p=0.513$ ). Three strokes occurred during the index hospitalisation, all in the noMAC group ( $p=0.504$ ).

### ECHOCARDIOGRAPHIC AND CLINICAL FOLLOW-UP

Median follow-up was 455 days (204-916) in the MAC group and 385 days (160-726) in the NoMAC group. At 30 days, most patients had experienced an improvement in MR severity of at least one grade (93% in both groups,  $p=0.576$ ), as well as an improvement in NYHA Functional Class of at least one grade (82% in both groups,  $p=0.567$ ), most (~80%) being in NYHA Functional Class  $\leq$  II ( $p=0.692$ ) (**Figure 1B**).

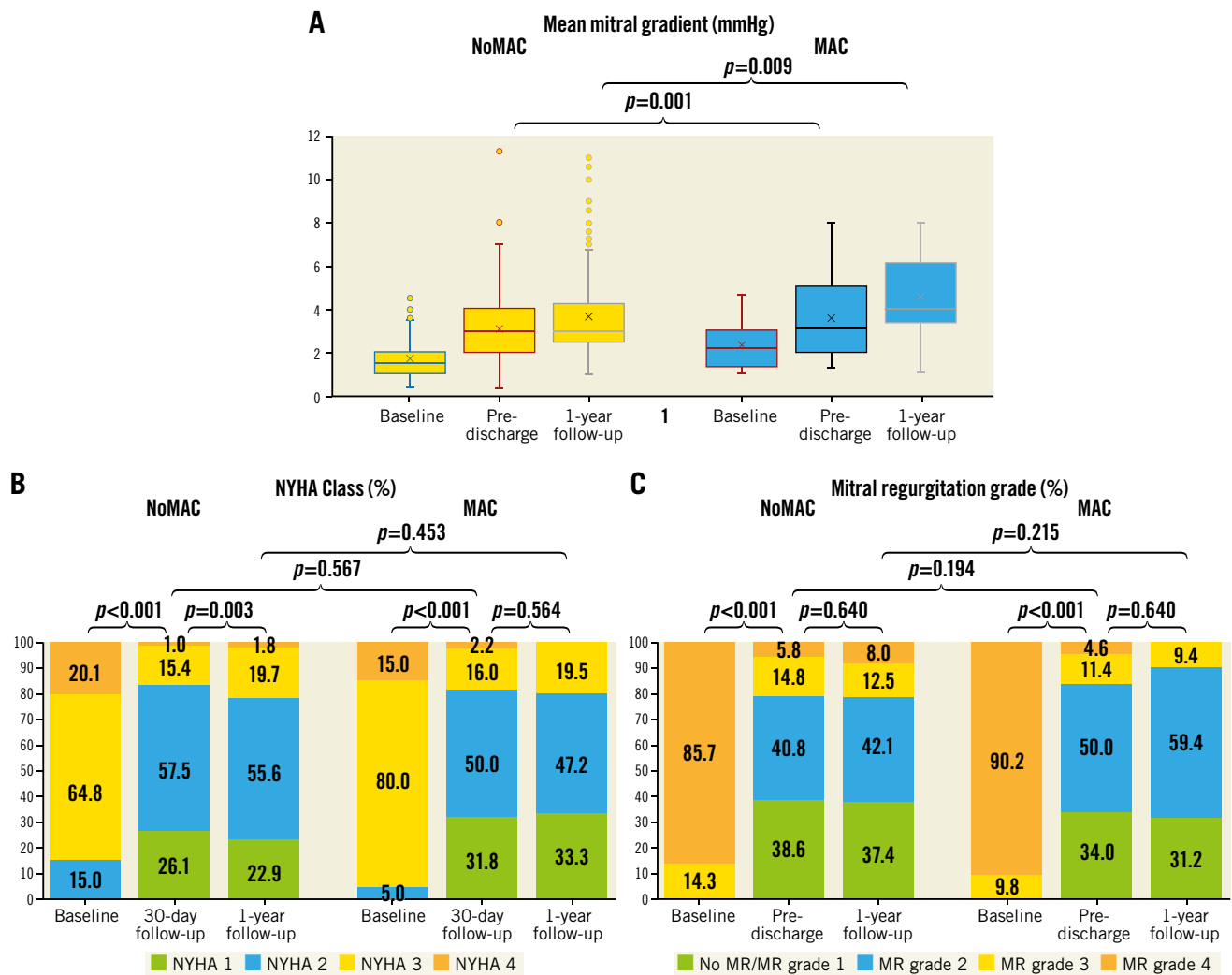
At one-year follow-up, 90.6% of MAC patients and 79.5% of NoMAC patients had residual MR grade 2 or less ( $p=0.129$ ) (**Figure 1C**). A reduction in SPAP was observed in both groups; there were no significant changes in LVEF between baseline and one-year follow-up echocardiogram (**Table 3**). Mean gradient after clip implantation increased significantly in both groups between discharge and one-year follow-up (**Table 3**). There was no association at Cox analysis between preprocedural mitral valve area, MR grade or LVEF changes with the increase of mean gradient at follow-up (hazard ratio [HR] 0.8, 95% confidence interval [CI]: 0.2-4.2,  $p=0.802$ ; HR 1, 95% CI: 0.9-1.1,  $p=0.787$ ; HR 0.92, 95% CI: 0.6-1.5,  $p=0.745$ , respectively). Only 9 patients (1.14%), all in the NoMAC group ( $p=0.250$ ), required reintervention during follow-up: 1 underwent a heart transplant, 2 had a mitral valve replacement, and 6 had a redo transcatheter mitral valve repair.

Clinically, patients remained in NYHA Functional Class II or less in 80.5% and 78.5% of MAC and NoMAC patients,

**Table 1. Baseline demographic and echocardiographic characteristics.**

|                                              |           | Overall<br>n=852 | No/mild MAC<br>n=791 | Moderate/severe MAC<br>n=61 | p-value          |
|----------------------------------------------|-----------|------------------|----------------------|-----------------------------|------------------|
| Severe MAC (%)                               |           | 19 (2.5)         | 0 (0)                | 19 (31.1)                   | N/A              |
| Age, years                                   |           | 73.2±10.4        | 72.8±10.4            | 78.3±8.7                    | <b>0.001</b>     |
| Sex, male (%)                                |           | 549 (64.4)       | 522 (66)             | 27 (44.3)                   | <b>0.001</b>     |
| BMI                                          |           | 27.1±4.8         | 27.1±4.8             | 27.7±5.3                    | 0.304            |
| Hypertension, n (%)                          |           | 631 (74.2)       | 585 (74)             | 46 (75.4)                   | 0.815            |
| Diabetes mellitus, n (%)                     |           | 363 (42.6)       | 339 (42.9)           | 24 (39.3)                   | 0.593            |
| GFR <60, n (%)                               |           | 427 (50.3)       | 390 (49.5)           | 37 (60.7)                   | 0.093            |
| Smoking, n (%)                               |           | 400 (47.1)       | 382 (48.5)           | 18 (29.5)                   | <b>0.004</b>     |
| Haemodialysis, n (%)                         |           | 22 (2.6)         | 20 (2.5)             | 2 (3.3)                     | 0.722            |
| Atrial fibrillation, n (%)                   |           | 499 (58.6)       | 460 (58.2)           | 39 (63.9)                   | 0.323            |
| Previous stroke, n (%)                       |           | 84 (9.9)         | 78 (9.9)             | 6 (9.8)                     | 0.990            |
| Ischaemic cardiomyopathy, n (%)              |           | 442 (51.9)       | 416 (52.7)           | 26 (42.6)                   | 0.131            |
| Previous PCI, n (%)                          |           | 292 (34.4)       | 278 (35.2)           | 14 (23)                     | 0.052            |
| Previous CABG, n (%)                         |           | 127 (15)         | 117 (14.9)           | 10 (16.4)                   | 0.751            |
| Previous valvular intervention, n (%)        |           | 104 (12.2)       | 89 (11.3)            | 15 (24.6)                   | <b>0.002</b>     |
| NYHA Class, n (%)                            | 1         | 0 (0)            | 0 (0)                | 0 (0)                       | <b>0.037</b>     |
|                                              | 2         | 121 (14.3)       | 118 (15)             | 3 (5)                       |                  |
|                                              | 3         | 557 (65.9)       | 509 (64.8)           | 48 (80)                     |                  |
|                                              | 4         | 167 (19.8)       | 158 (20.1)           | 9 (15)                      |                  |
| Previous year heart failure admission, n (%) |           | 549 (64.6)       | 515 (65.2)           | 34 (56.7)                   | 0.183            |
| STS score                                    |           | 3 (2-6)          | 3 (2-6)              | 4 (3-7)                     | <b>0.027</b>     |
| EuroSCORE II                                 |           | 5 (2.9-8.4)      | 4.9 (2.8-8.4)        | 5.6 (4-10.6)                | 0.260            |
| LVEF (%)                                     |           | 41.3±15.2        | 40.4±15              | 52.5±12.3                   | <b>&lt;0.001</b> |
| EDLVD, mm                                    |           | 60.2±10.3        | 60.8±10.2            | 53.1±8.9                    | <b>&lt;0.001</b> |
| ESLVD, mm                                    |           | 43.9±13.5        | 44.9±13.4            | 34.9±10.6                   | <b>&lt;0.001</b> |
| MR grade, n (%)                              | 1-2       | 0 (0)            | 0 (0)                | 0(0)                        | 0.336            |
|                                              | 3         | 118 (14)         | 112 (14.3)           | 6 (9.9)                     |                  |
|                                              | 4         | 728 (86.1)       | 673 (85.7)           | 55 (90.2)                   |                  |
| MR mechanism, n (%)                          | Primary   | 261 (30.7)       | 237 (30.1)           | 24 (39.3)                   | 0.108            |
|                                              | Secondary | 458 (54)         | 433 (55)             | 25 (41)                     |                  |
|                                              | Mixed     | 130 (15.3)       | 118 (15)             | 12 (19.7)                   |                  |
| Subvalvular apparatus calcification, n (%)   |           | 58 (7.1)         | 37 (4.9)             | 21 (35.6)                   | <b>&lt;0.001</b> |
| Posterior leaflet restriction, n (%)         |           | 394 (46.5)       | 369 (46.9)           | 25 (41)                     | 0.373            |
| Eccentric jet, n (%)                         |           | 266 (33)         | 233 (31.3)           | 33 (54.1)                   | <b>&lt;0.001</b> |
| Multiple jets, n (%)                         |           | 98 (12.4)        | 88 (12.1)            | 10 (16.4)                   | 0.330            |
| EROA, cm <sup>2</sup>                        |           | 0.5±0.2          | 0.5±0.3              | 0.7±0.3                     | <b>0.002</b>     |
| Mitral mean gradient, mmHg                   |           | 1.8±0.9          | 1.7±0.8              | 2.3±1                       | <b>&lt;0.001</b> |
| Mitral valvular area, cm <sup>2</sup>        |           | 5.3±1.2          | 5.3±1.3              | 4.9±0.9                     | 0.088            |
| Systolic pulmonary artery pressure, mmHg     |           | 50.7±17.1        | 50.7±16.8            | 50.4±20.7                   | 0.903            |
| Anterior leaflet thickness, mm               |           | 2.6 ±1.3         | 2.6±1.3              | 2.6±1.4                     | 0.972            |
| Posterior leaflet thickness, mm              |           | 2.4± 1.3         | 2.4±1.3              | 2.4±1.3                     | 0.804            |
| Anterior leaflet length, mm                  |           | 21.1±6.3         | 21.2±6.2             | 19.8±6.9                    | 0.082            |
| Posterior leaflet length, mm                 |           | 11.7±2.8         | 11.7±2.8             | 11.6±3.5                    | 0.679            |
| Coaptation length, mm                        |           | 2.9±1.7          | 3±1.7                | 2.5±1.7                     | 0.060            |
| Coaptation height, mm                        |           | 8.3±3.7          | 8.4±3.8              | 7±3.5                       | <b>0.008</b>     |

BMI: body mass index; CABG: coronary artery bypass grafting; EDLVD: end-diastolic left ventricular diameter; EROA: effective regurgitant orifice area; ESLVD: end-systolic left ventricular diameter; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; MAC: mitral annular calcification; MR: mitral regurgitation; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons



**Figure 1.** Haemodynamic and clinical follow-up. A) Changes over time in mean mitral gradient during follow-up according to mitral annulus calcification (MAC) grade. B) Changes over time in New York Heart Association (NYHA) Functional Class during follow-up according to MAC grade. C) Changes over time in mitral regurgitation (MR) grade during follow-up according to MAC grade.

respectively ( $p=0.453$ ) (Figure 1B). Along with NYHA Class improvement, a global reduction in readmissions for heart failure within the year post MitraClip procedure was observed (21.3% vs 14.4%,  $p=0.145$ , for the MAC and NoMAC groups, respectively), translating into a reduction of almost 78% and 65%, respectively ( $p=0.145$ ), as compared to the year before the procedure.

There were 11 patients in the MAC group for whom two years of follow-up data were available: 72.7% of them maintained an MR grade of 2 or less and an NYHA Class II or less. None of them required any additional mitral intervention during this period.

At one year, all-cause mortality was higher among MAC patients (19.7% vs 11.3%,  $p=0.050$ ), with no differences in cardiovascular mortality (15.3% vs 9.2%,  $p=0.129$ ). Of the 101 deaths within the first year of follow-up, 79 were cardiovascular and 22 were non-cardiovascular. Adjusted Cox model regression survival analysis showed that there was a marginal correlation of MAC with one-year all-cause mortality (HR 2, 95% CI: 0.9-4.3,  $p=0.070$ ) but not

with cardiovascular mortality (HR 2, 95% CI: 0.8-5.1,  $p=0.123$ ) or unplanned cardiovascular readmission (HR 1.5, 95% CI: 0.8-3,  $p=0.210$ ). Mean gradient of  $\geq 5$  mmHg at discharge was also not an independent predictor of all-cause or cardiovascular mortality (HR 2.1, 95% CI: 0.5-8.6,  $p=0.321$ , and HR 1.3, 95% CI: 0.5-3.2,  $p=0.624$ , respectively) or an independent predictor of unplanned cardiovascular rehospitalisation (HR 0.8, 95% CI: 0.31-2.00,  $p=0.633$ ) in the MAC cohort.

As shown by Kaplan-Meier curves at one-year follow-up (Figure 2), there was a higher all-cause mortality risk in MAC patients ( $p=0.030$ ) with no significant differences between groups in cardiovascular mortality ( $p=0.159$ ) and rehospitalisation due to heart failure ( $p=0.115$ ).

## Discussion

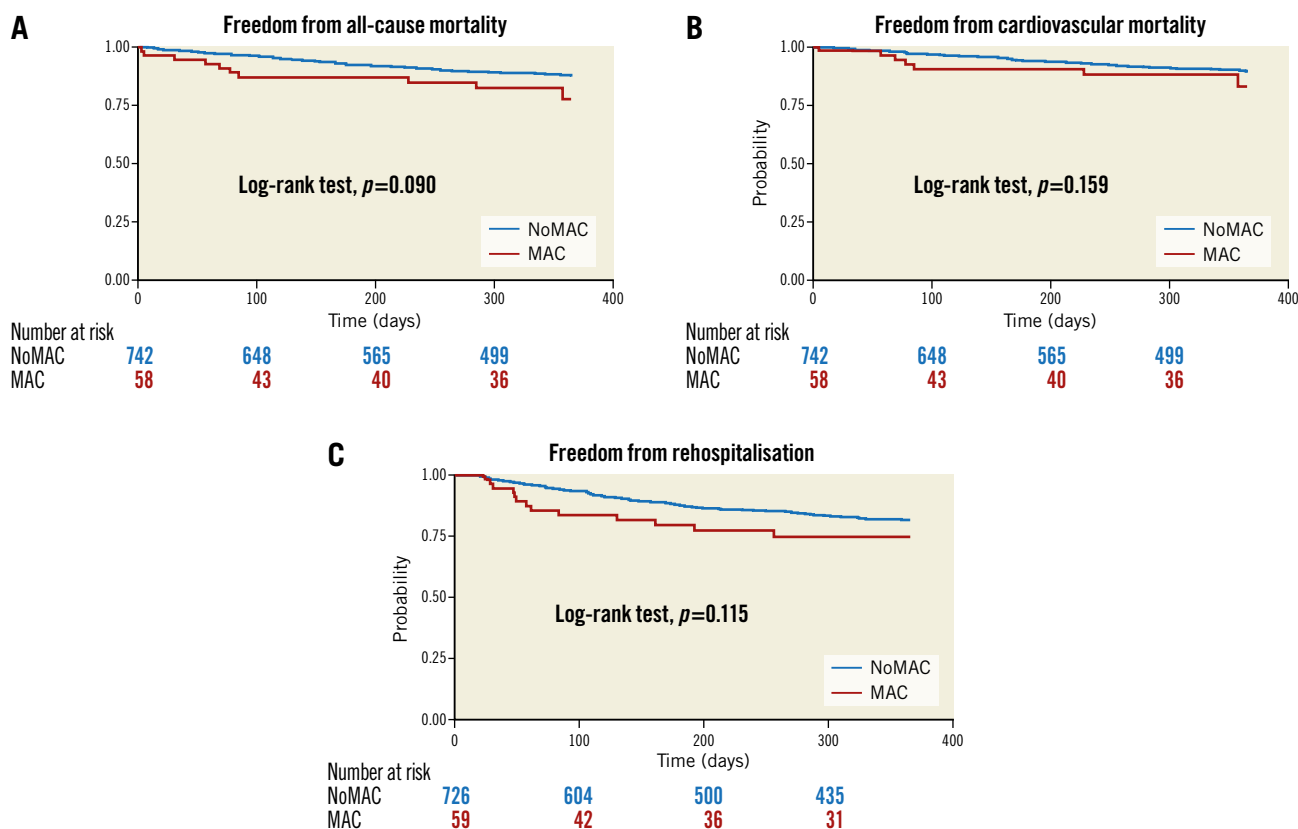
The main findings of this study are the following: 1) Transcatheter edge-to-edge repair with the MitraClip system in selected patients

**Table 2. Procedural and in-hospital outcomes.**

|                                                                                                               |    | Overall<br>n=852 | No/mild MAC<br>n=791 | Moderate/severe MAC<br>n=61 | p-value      |
|---------------------------------------------------------------------------------------------------------------|----|------------------|----------------------|-----------------------------|--------------|
| Procedure duration, min                                                                                       |    | 136±66           | 135±66               | 144±61                      | 0.327        |
| Technical success, n (%)                                                                                      |    | 833 (97.9)       | 775 (98.1)           | 58 (95.1)                   | 0.114        |
| Procedural success, n (%)                                                                                     |    | 807 (94.8)       | 751 (95.1)           | 56 (91.8)                   | 0.268        |
| Number of clips, n (%)                                                                                        | 1  | 497 (56.7)       | 455 (57.9)           | 42 (68.9)                   | 0.474        |
|                                                                                                               | 2  | 290 (34.2)       | 275 (35)             | 15 (24.6)                   |              |
|                                                                                                               | 3  | 57 (6.7)         | 53 (6.7)             | 4 (6.6)                     |              |
|                                                                                                               | ≥4 | 2 (0.3)          | 2 (0.3)              | 0 (0)                       |              |
| Partial/complete detachment, n (%)                                                                            |    | 19 (2.2)         | 19 (2.4)             | 0 (0)                       | 0.224        |
| Embolisation, n (%)                                                                                           |    | 0 (0)            | 0 (0)                | 0 (0)                       | N/A          |
| Chord rupture, n (%)                                                                                          |    | 6 (0.7)          | 5 (0.6)              | 1 (1.7)                     | 0.357        |
| Conversion to surgery, n (%)                                                                                  |    | 7 (0.8)          | 5 (0.6)              | 2 (3.3)                     | <b>0.027</b> |
| Major bleeding MVARC scale, n (%)                                                                             |    | 39 (4.6)         | 38 (4.8)             | 1 (1.6)                     | 0.254        |
| Cardiac tamponade, n (%)                                                                                      |    | 7 (0.8)          | 7 (0.9)              | 0 (0)                       | 0.461        |
| Residual MR grade, n (%)                                                                                      | 0  | 30 (3.6)         | 28 (3.6)             | 2 (3.3)                     | 0.194        |
|                                                                                                               | 1  | 446 (52.8)       | 420 (53.6)           | 26 (42.6)                   |              |
|                                                                                                               | 2  | 308 (36.5)       | 281 (35.9)           | 27 (44.3)                   |              |
|                                                                                                               | 3  | 45 (5.3)         | 42 (5.4)             | 3 (4.9)                     |              |
|                                                                                                               | 4  | 15 (1.8)         | 12 (1.5)             | 3 (4.9)                     |              |
| Residual mitral mean gradient, mmHg                                                                           |    | 3.1±1.6          | 3±1.3                | 3.6±1.3                     | <b>0.001</b> |
| In hospital mortality, n (%)                                                                                  |    | 7 (0.8)          | 6 (0.8)              | 1 (1.6)                     | 0.513        |
| Stroke, n (%)                                                                                                 |    | 3 (0.4)          | 3 (0.4)              | 0                           | 0.504        |
| MAC: mitral annular calcification; MR: mitral regurgitation; MVARC: Mitral Valve Academic Research Consortium |    |                  |                      |                             |              |

**Table 3. Echocardiographic changes over time compared by paired samples.**

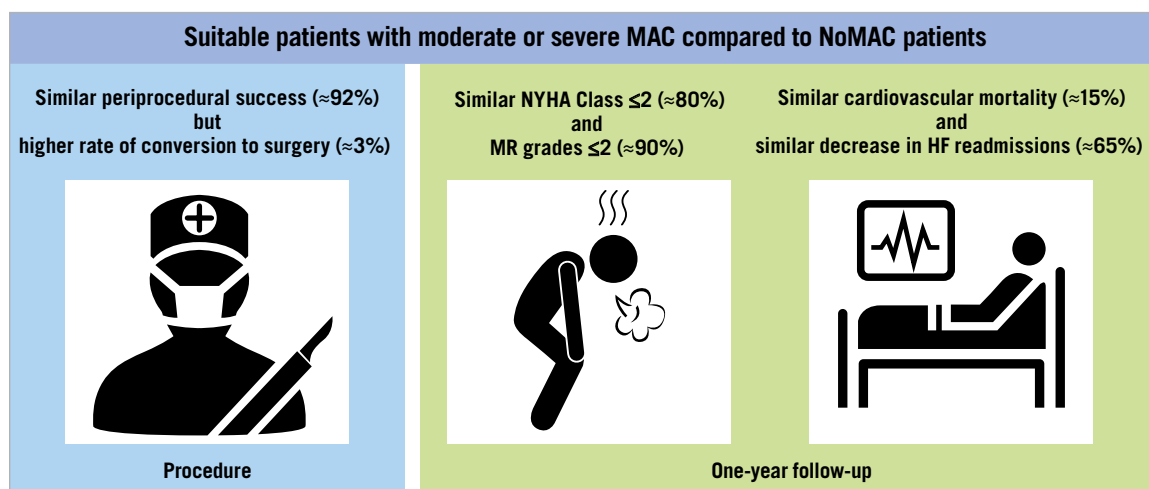
|                                                                                                                                                                                                                                                   |       | Baseline<br>(NoMAC= 791 MAC=61) | Discharge<br>(NoMAC=785 MAC=59) | 1-year follow-up<br>(NoMAC=361 MAC=32) | p-value          | Inter<br>p-value |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|---------------------------------|---------------------------------|----------------------------------------|------------------|------------------|
| TDLVD, mm                                                                                                                                                                                                                                         | NoMAC | 60.8±10.2                       |                                 | 58.8±10.5                              | <b>&lt;0.001</b> | 0.958            |
|                                                                                                                                                                                                                                                   | MAC   | 53.1±8.9                        |                                 | 54±9.1                                 | 0.060            |                  |
| TSLVD, mm                                                                                                                                                                                                                                         | NoMAC | 44.9±13.4                       |                                 | 44.2±14                                | 0.815            | 0.765            |
|                                                                                                                                                                                                                                                   | MAC   | 34.9±10.6                       |                                 | 37.3±7                                 | 0.442            |                  |
| LVEF, %                                                                                                                                                                                                                                           | NoMAC | 40.4±15                         |                                 | 40.5±15                                | 0.621            | 0.551            |
|                                                                                                                                                                                                                                                   | MAC   | 52.5±12.3                       |                                 | 52.8±15.9                              | 0.563            |                  |
| Systolic pulmonary artery pressure, mmHg                                                                                                                                                                                                          | NoMAC | 50.7±16.8                       |                                 | 43.3±14.2                              | <b>&lt;0.000</b> | 0.055            |
|                                                                                                                                                                                                                                                   | MAC   | 50.4±20.7                       |                                 | 40±15.7                                | <b>0.017</b>     |                  |
| Mitral mean gradient, mmHg                                                                                                                                                                                                                        | NoMAC | 1.7±0.8                         | 3±1.3                           |                                        | <b>&lt;0.001</b> | <b>0.049</b>     |
|                                                                                                                                                                                                                                                   | MAC   | 2.3±1                           | 3.6±1.3                         |                                        | <b>&lt;0.001</b> |                  |
|                                                                                                                                                                                                                                                   | NoMAC |                                 | 3±1.3                           | 3.6±1.7                                | <b>&lt;0.001</b> | 0.894            |
|                                                                                                                                                                                                                                                   | MAC   |                                 | 3.6±1.3                         | 4.6±2.1                                | <b>0.036</b>     |                  |
| Residual MR, % ≤2                                                                                                                                                                                                                                 | NoMAC | 0                               | 93.1                            |                                        | <b>&lt;0.001</b> | 0.446            |
|                                                                                                                                                                                                                                                   | MAC   | 0                               | 90.2                            |                                        | <b>&lt;0.001</b> |                  |
|                                                                                                                                                                                                                                                   | NoMAC |                                 | 93.1                            | 78.7                                   | 0.815            | 0.778            |
|                                                                                                                                                                                                                                                   | MAC   |                                 | 90.2                            | 93.8                                   | 0.500            |                  |
| LVEF: left ventricular ejection fraction; MAC: mitral annular calcification, NoMAC: no/mild mitral annular calcification; MR: mitral regurgitation; TDLVD: telediastolic left ventricular diameter; TSLVD: telesystolic left ventricular diameter |       |                                 |                                 |                                        |                  |                  |



**Figure 2.** One-year survival curves for the composite event (A) all-cause mortality, (B) cardiovascular-related mortality, and (C) freedom from heart failure rehospitalisation, according to MAC grade.

with moderate or severe MAC is comparable to patients without MAC in terms of feasibility, as demonstrated by the high technical success rate and the low incidence of procedural complications, despite a higher rate of conversion to surgery. 2) At one-year follow-up, the durability of the repair in selected patients with moderate or severe MAC is similar to that in those without MAC. 3) As expected, mean mitral gradients after

MitraClip implantation were higher in MAC patients but it this did not imply significantly worse outcomes in terms of mortality or unplanned cardiac readmissions. 4) Patients with moderate or severe MAC also benefitted clinically from this procedure, as they experienced significant and sustained improvement in symptoms and no significant differences in cardiovascular mortality at one year (**Central illustration**).



**Central illustration.** Transcatheter edge-to-edge mitral valve repair in patients with mitral annulus calcification.

Patients with severe MR and MAC represent a major surgical challenge as MAC implies complex surgery and a higher rate of post-operative complications and, in some series, repair failure<sup>10-18</sup>. Therefore, a need for less invasive and yet efficient alternative therapies arises. The MitraClip system has become an effective alternative to open heart surgery for treating MR in high surgical risk patients<sup>20-26</sup>. However, even though MAC patients are often turned down for mitral valve surgery, they are also typically excluded from randomised clinical trials and from early feasibility studies with transcatheter mitral valve replacement therapies.

To date, only one single-centre study has assessed the safety of mitral valve repair with the MitraClip system in patients with MAC<sup>33</sup>. A total of 28 patients with moderate or severe MAC were assessed, showing high procedural success and similar improvements in MR grade and Functional Class, as compared to patients with no or mild MAC.

To date, the present study constitutes the largest multicentre experience conducted with the MitraClip device in patients with significant concomitant MAC and MR. In our study, from a cohort of 852 patients, 61 patients were found to have moderate or severe MAC on the preprocedural echocardiogram, 19 (31%) of whom had severe MAC. From a clinical standpoint, MAC patients were older and had a more advanced Functional Class. They also exhibited higher preprocedural transvalvular gradients along with larger EROAs despite there being no differences in mitral valve area, potentially implying a greater MR in this group. However, this could also reflect a different haemodynamic situation, as these patients have smaller ventricles with higher LVEFs. Of note, percutaneous repair was feasible in the vast majority of patients, with 98% technical success and 95% procedural success, in line with previous studies with the MitraClip device<sup>20-26</sup>. Only 5 patients with moderate or severe MAC had an unsuccessful procedure: 2 of them experienced a posterior leaflet tear and massive MR that led to emergent cardiac surgery, and for the remaining 3 patients, a reduction in MR grade  $\leq 2+$  could not be achieved. Both patients who experienced a posterior leaflet tear presented moderate MAC with no extension to the subvalvular apparatus, neither of them had a short or restrictive posterior leaflet, or calcified or thin leaflets. As for the 3 patients in whom an MR grade  $\leq 2$  could not be achieved, 2 of them presented severe MAC and subvalvular apparatus calcification and a preprocedural mitral gradient of 3 mmHg and only a final MR grade 3 could be obtained with a final post-procedural gradient of 6 and 4 mmHg, respectively. The third patient had moderate MAC with no extension to the subvalvular apparatus but had multiple jets. In that patient, finally no clip was implanted, as a satisfactory reduction of MR grade could not be achieved. Larger studies are needed to determine predictors of success in this population. However, the overall results obtained in this study are encouraging considering that patients with MAC exhibited more complex anatomies (increased subvalvular apparatus calcification and more eccentric jets) and higher MR grades.

As expected, immediate post-procedural gradients were significantly higher in MAC patients:  $\geq 5$  mmHg in 18.5% of them

but  $< 8$  mmHg in all cases. Nonetheless, even although a residual gradient  $\geq 5$  mmHg has been previously described as a potential predictor of worse clinical outcomes, in our cohort it was not independently associated with an increase in all-cause or cardiovascular mortality or unplanned cardiac readmissions at follow-up, in line with the results obtained in the COAPT trial<sup>34,35</sup> (see also R. Halaby, Lack of association of mitral valve gradient after MitraClip with outcomes in functional mitral regurgitation: results from the COAPT trial. Presented at ACC.20 World Congress of Cardiology Virtual, March 29, 2020). The mean gradient after clip implantation also increased significantly in both groups between discharge and one-year follow-up (**Table 3**). There are some possible explanations for this, e.g., improvement in LVEF or decrease in mitral valve area, but none of them could be proven in our cohort as we found no association at Cox analysis between the former variables and mean gradient at follow-up.

Importantly, in the MAC group, there were no cases of clip detachment, embolisation or stroke, and only one in-hospital death. However, there was a higher conversion to cardiac surgery (3.28%) during index hospitalisation than in the NoMAC group due, in the two patients that experienced this complication, to posterior leaflet tear that led to massive MR. Nonetheless, overall these results are remarkable considering the relatively higher periprocedural mortality rates observed in the early experience with transcatheter mitral valve replacement (up to 14% vs 1.6% in the MAC group of the present study), which may be considered as another interesting alternative in the presence of moderate or severe MAC and risk of left ventricular outflow tract obstruction<sup>36-39</sup>.

Repair durability in this setting might have been considered an important concern. This is based on the absence of long-term durability data for transcatheter mitral valve repair in such patients and also on the basis of an unfavourable surgical predicate with the Alfieri technique in this setting, which resulted in higher gradients, reduced durability and increased need for reoperation<sup>27</sup>. Nonetheless, in our study, transcatheter mitral repair with the MitraClip device in MAC patients resulted in sustained clinical and echocardiographic improvements at one-year follow-up, with 80% of patients remaining at NYHA Functional Class I-II and with a residual MR  $\leq 2$  in 91% of MAC patients. Importantly, no reintervention was required in those patients within the first year after the MitraClip procedure (0% in the MAC group, 1.1% in the NoMAC group).

Overall, these findings translated into a substantial reduction in the number of heart failure-related rehospitalisations following the procedure, as compared to the number of admissions of these patients the year before the MitraClip procedure was performed, similar to the benefit observed in patients without MAC. This clinical and echocardiographic benefit was also maintained in the 11 MAC patients for whom two years of follow-up data were available: an NYHA Class I or II was still observed in 72.7% of them along with an MR grade of 2 or less in 72.7%, without



any additional mitral intervention during this period. These results reinforce the potential use of transcatheter edge-to-edge repair to treat symptomatic patients with high grade MR at increased surgical risk and severely calcified mitral valve annulus, in the absence of significant mitral stenosis or leaflet calcification.

There was a marginal correlation of all-cause mortality with MAC patients, even though MAC was not found to be an independent predictor for all-cause or cardiovascular mortality at one year. It is noteworthy that MAC patients are often elderly, with increased morbidity, mortality and cardiovascular disease, often making them ineligible for open heart surgery due to pre-existing comorbidities or technical reasons (high calcium burden). Hence, this association is probably due to a higher comorbidity burden in these patients, rather than the procedure itself, which carried a low rate (<2%) of in-hospital mortality.

Overall, use of the MitraClip device in patients with significant annular calcification resulted in significant clinical improvement with durable reduction of MR at one year. Our results highlight the safety and efficacy as well as the one-year durability of transcatheter edge-to-edge repair in patients with MAC. This constitutes a reasonable alternative to surgery in this subgroup of patients and may probably be considered the first choice therapy in patients ineligible for surgery and with favourable anatomy for percutaneous edge-to-edge repair.

## Limitations

Our study had several limitations. First, it was a retrospective observational multicentre study which has limitations inherent to its nature. In addition, the grading of MAC was qualitative and based on echocardiography, with no centralised core laboratory adjudication of echocardiographic data or clinical events. Second, medical treatment before and after the procedure was not systematically recorded and may have influenced post-operative outcomes. Finally, the study population was limited to one specific type of transcatheter edge-to-edge repair device (MitraClip); therefore, the results may not be generalisable to other edge-to-edge therapies. Of note, the study was conducted in a highly selected MAC population and the procedures were performed in highly experienced centres. Thus, further research is required before generalising these results.

## Conclusions

Percutaneous repair with the MitraClip system in patients with significant MAC and high surgical risk is safe and feasible, with sustained improvement in NYHA Functional Class and MR reduction at one year in the vast majority of patients (~80%). These results suggest that percutaneous edge-to-edge repair may be considered as a valid alternative to surgery in selected patients with severe MR and MAC, in the absence of significant mitral stenosis or leaflet calcification. Further evaluation in larger-scale trials is required to determine predictors of procedural success and long-term outcomes in MAC patients treated with the MitraClip system.

## Impact on daily practice

MAC is a condition commonly found in patients affected with severe MR that is associated with a high morbidity and mortality and worse surgical outcomes. Therefore, the need for a less invasive and yet efficient alternative to surgery arises in this setting. In this study, transcatheter edge-to-edge repair with the MitraClip system in selected patients with moderate or severe MAC was found to be a safe and feasible alternative that achieved a significant reduction of MR grade and a substantial clinical improvement at one-year follow-up. Thus, MitraClip implantation emerges as a valid therapeutic option in this population, even though larger studies are needed in order to determine predictors of good clinical outcomes.

## Conflict of interest statement

R.D. Estevez-Loureiro, L. Nombela-Franco, L. Sanchis, C-H. Li and D. Arzamendi have served as proctors for Abbott Vascular. X. Freixa, R. Estévez-Loureiro, and L. Nombela-Franco are consultants for Abbott Vascular and have received personal fees from Abbott. C-H. Li has received personal fees from Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## 4.2. Artículo 2

Global longitudinal strain predicts outcomes in patients with reduced left ventricular function undergoing transcatheter edge-to-edge mitral repair

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## Article

# Global Longitudinal Strain Predicts Outcomes in Patients with Reduced Left Ventricular Function Undergoing Transcatheter Edge-to-Edge Mitral Repair

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**Abstract:** Background: The timing and selection of optimal candidates for mitral transcatheter edge-to-edge valve repair remains to be fully determined, especially in cases with severely depressed left ventricular ejection fraction (LVEF). The objective of this study is to evaluate the prognostic value of myocardial strain (LVGLS) in this setting. Methods: Retrospectively, 172 consecutive patients with LVEF  $\leq 40\%$  and severe MR treated with MitraClip were included. Four groups were generated according to the LVEF ( $<30\%$  or  $\geq 30\%$ ) and median LVGLS. The primary end-point was cardiovascular mortality. Results: Procedural success was high (96.5%) and complications were rare. At one-year follow-up, 82.5% of patients maintained MR grade  $\leq 2$ , 79.2% were at a NYHA class  $\leq II$  and a reduction of 80% in heart failure admissions was observed in all groups. Interestingly, among patients with a more depressed LVEF, LVGLS was found to be an independent predictor for cardiovascular mortality (HR: 3.3; 95% CI: 1.1–10,  $p = 0.023$ ). Conclusions: Mitral valve repair with MitraClip is safe and it improves the mid-term functional class of patients regardless of LVEF. LVGLS can help in the selection of optimal candidates and timing for this procedure, as well as in the recognition of those patients with worse prognoses.

**Keywords:** Mitral regurgitation; left ventricular global longitudinal strain; MitraClip

## 1. Introduction

Mitral valve regurgitation (MR) is nowadays the second most common valvular heart disease and is associated with a deterioration of the quality and expectancy of life of those who suffer from this condition. The European Society of Cardiology recommends surgical treatment if severe and symptomatic MR is present or if there are signs of advanced impact of the disease such as the development of atrial fibrillation, pulmonary artery hypertension or enlargement of the left ventricle or atrium [1]. However, a non-neglectable percentage of these patients are deemed to be at high surgical risk due to comorbidities or reduced left ventricular ejection fraction (LVEF) [2].

The MitraClip System (Abbott Vascular, Abbot Park, Illinois), a transcatheter technique that mimics the Alfieri stitch [3] has arisen as an alternative to surgery for high-risk patients

and has demonstrated its safety and efficacy in reducing MR severity and improving symptoms and quality of life [4–7]. In recent years, there has been a growing interest in defining the optimal candidates and timing for this therapy, particularly since the controversial results from MITRAFR (Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trials were reported [8–10]. It has been hypothesized that there could be a “point of no return” at which this therapy may lack clinical benefit despite being technically feasible [11]. This may be of special interest in the presence of reduced LVEF where the possibility of determining the potential ability of the myocardium to adapt to new loading conditions after MitraClip implantation may identify good candidates for the procedure. In this regard, assessing the myocardial deformation through the quantification of the strain, a parameter that is less affected by preload and afterload and more reproducible [12,13] could add incremental value to the decision-making process [14–18].

This study sought to evaluate the potential predictor capacity of myocardial strain in patients affected with severe MR and reduced LVEF undergoing mitral transcatheter edge-to-edge repair (M-TEER) with the MitraClip System.

## 2. Materials and Methods

Data was obtained from the Spanish MitraClip multicenter registry which included all consecutive patients affected with symptomatic MR grade  $\geq 3$  undergoing M-TEER since June 2012 in 24 participating centers. This study evaluated the data from all patients with baseline LVEF  $\leq 40\%$  enrolled in five of these institutions. All patients were deemed to be at high risk for surgery and considered for percutaneous repair after evaluation by the local Heart Team. The study was performed in accordance with the local ethics committee and all patients signed informed consent for the procedure.

Baseline demographic parameters included age, gender, weight, height, hypertension, diabetes mellitus, renal impairment, chronic hemodialysis, smoking, atrial fibrillation, previous cerebrovascular disease, ischemic heart disease, New York Heart Association (NYHA) functional class, Society of Thoracic Surgeons (STS) score, and heart failure hospitalization during the year prior to the procedure. Patients were considered to be under optimal medical treatment if in compliance with the guidelines valid at the time of the procedure.

Baseline echocardiographic parameters were based on pre-procedural transthoracic (TTE) and transesophageal (TEE) echocardiography following the European Association of Cardiovascular Imaging recommendations [19,20] and performed by the local expert on cardiovascular imaging. Left ventricular ejection fraction (LVEF) was assessed by echocardiography using the biplane Simpson method. The severity of pre-procedural MR was assessed taking into account color flow Doppler, vena contracta width, the flow convergence method, pulmonary venous flow and continuous wave doppler. Post-procedural or residual MR was assessed taking into account the number of jets, color flow doppler, vena contracta width, continuous wave doppler and pulmonary venous flow [21]. Strain analysis was performed offline using 2D strain imaging software QLAB Advanced Quantification Software 13.0, Koninklijke Philips Electronics NV 2019 and the General Electric Automated Function Imaging software. The software automatically traced the endocardial borders at the end of systole with further manual adjustments if necessary to optimized automated speckle tracking.

Technical success was defined as the correct implantation of at least one device and the absence of procedural mortality or emergent cardiovascular intervention related to the procedure while procedural success was defined as the achievement of MR grade reduction to 2 or less [22]. Procedure-related bleeding and its severity were defined according to the BARC (Bleeding Academic Research Consortium) criteria [22].

NYHA class, MR grade, mean mitral gradient, pulmonary artery systolic pressure (SPAP), LVEF, left and right ventricular dimensions, left atrial volume and left ventricular

global longitudinal strain (LVGLS) were recorded as well as the need for subsequent mitral valve surgery, heart transplant, heart failure rehospitalization and mortality. Major composite clinical events (MACE) were a composite of cardiovascular death and rehospitalization due to heart failure at follow-up.

The assessment of normality was performed using the Shapiro–Wilk test. Results are presented as the mean (standard deviation) for continuous variables with a normal distribution, the median (interquartile range) for continuous variables with a non-Gaussian distribution, and with counts and percentages in the case of categorical variables. We divided our cohort into four groups according to the degree of LV dysfunction (severe dysfunction if LVEF was below 30% or moderate dysfunction if LVEF was above or equal to 30%) and LVGLS median value ( $-8.4\%$ ). Group 1 was comprised of patients with an LVEF above 30% and an LVGLS  $< -8.4\%$ ; group 2 included patients with LVEF  $< 30\%$  and LVGLS  $< -8.4\%$ ; group 3 restrained patients with LVEF  $\geq 30\%$  and LVGLS  $\geq -8.4\%$ ; and group 4 incorporated patients with LVEF  $< 30\%$  and LVGLS  $\geq -8.4\%$ . Differences between groups were tested using the chi-square test for categorical variables and Student's *t* and ANOVA tests for continuous variables. A 95% level of significance was applied ( $p < 0.05$ ). Kaplan–Meier survival estimator was used to determine the time to MACE at follow-up. Data from survival curves and event-free survival rates along with the long-rank test were used for comparison between groups. Multivariate analysis testing the association of the different parameters studied was performed using Cox proportional hazard modeling. For data analysis, the STATA 13.1 version statistical package was used (StataCorp LP, College Station, TX, USA).

### 3. Results

#### 3.1. Baseline Results

A total of 275 patients with symptomatic MR and LVEF  $\leq 40\%$  were treated with the MitraClip system during the study period. Patients with unavailable baseline LVGLS were excluded ( $n = 103$ ) resulting in a final study population of 172 patients. Baseline demographic and clinical characteristics are shown in Table 1. Most patients were male (73.4%), smokers (57.8%), and presented with hypertension (70.5%) as well as a history of ischemic cardiomyopathy (63%). The majority were at NYHA class III or IV at baseline (58.1% and 23.9%, respectively), and up to 82.1% had been hospitalized due to heart failure in the year prior to the intervention. There were no differences between groups in baseline clinical characteristics.

**Table 1.** Basal demographic and clinical characteristics.

|                                    | Overall        | Group 1 $n = 55$ | Group 2 $n = 31$ | Group 3 $n = 41$ | Group 4 $n = 46$ | <i>p</i> |
|------------------------------------|----------------|------------------|------------------|------------------|------------------|----------|
| Age (years)                        | 72.5 $\pm$ 9.6 | 75.5 $\pm$ 9.6   | 70.3 $\pm$ 8.2   | 71.7 $\pm$ 11.4  | 72.4 $\pm$ 8.3   | 0.133    |
| Sex (Male %)                       | 73.4           | 70.9             | 64.5             | 80.5             | 76.1             | 0.448    |
| Hypertension (%)                   | 70.5           | 70.9             | 61.3             | 73.2             | 73.9             | 0.644    |
| Diabetes Mellitus (%)              | 46.8           | 45.5             | 58.0             | 41.5             | 45.7             | 0.549    |
| Glomerular filtrate rate $<60$ (%) | 47.7           | 49.1             | 63.3             | 41.5             | 41.3             | 0.224    |
| Smoking (%)                        | 57.8           | 56.4             | 70.9             | 63.4             | 45.7             | 0.135    |
| Hemodialysis (%)                   | 0.6            | 0.0              | 3.2              | 0.0              | 0.0              | 0.203    |
| Atrial Fibrillation (%)            | 54.3           | 65.5             | 45.2             | 46.3             | 54.4             | 0.183    |
| Previous stroke (%)                | 14.5           | 18.2             | 6.5              | 14.6             | 15.2             | 0.523    |
| Ischemic cardiomyopathy (%)        | 63             | 61.8             | 54.8             | 75.6             | 58.7             | 0.237    |
| Previous PCI (%)                   | 41.3           | 29.1             | 43.3             | 53.7             | 43.5             | 0.107    |

Table 1. Cont.

|                                           | Overall             | Group 1 n = 55        | Group 2 n = 31      | Group 3 n = 41      | Group 4 n = 46      | p     |
|-------------------------------------------|---------------------|-----------------------|---------------------|---------------------|---------------------|-------|
| Previous CABG (%)                         | 17.3                | 14.6                  | 9.7                 | 19.5                | 23.9                | 0.378 |
| Previous valvular intervention (%)        | 10.4                | 5.5                   | 6.5                 | 14.6                | 15.2                | 0.273 |
| NYHA Class (%)                            |                     |                       |                     |                     |                     | 0.899 |
| 1                                         | 0                   | 0.0                   | 0.0                 | 0.0                 | 0.0                 |       |
| 2                                         | 18                  | 18.2                  | 19.3                | 22.5                | 13.0                |       |
| 3                                         | 58.1                | 61.8                  | 58.1                | 52.5                | 58.7                |       |
| 4                                         | 23.9                | 20.0                  | 22.6                | 25.0                | 28.3                |       |
| Previous Year Heart Failure Admission (%) | 82.1                | 80.0                  | 80.7                | 82.9                | 84.8                | 0.929 |
| ProBNP                                    | 5278<br>(2810–7990) | 4803.5<br>(1892–8648) | 5509<br>(5017–6002) | 6012<br>(3000–9210) | 2899<br>(2515–6104) | 0.777 |
| STS score                                 | 4.6 ± 3.5           | 4.6 ± 3.1             | 3.3 ± 2.4           | 4.6 ± 3.7           | 5.0 ± 4.2           | 0.406 |
| EuroScore II                              | 8.3 ± 5.5           | 7.2 ± 5.8             | 7.0 ± 5.0           | 8.2 ± 7.7           | 9.8 ± 5.5           | 0.377 |

PCI: percutaneous cardiac intervention; CABG: coronary artery bypass grafting; NYHA: New York Heart Association; ProBNP: pro-brain natriuretic peptide; STS: Society of Thoracic Surgeons.

Baseline echocardiographic parameters are summarized in Table 2. All patients had an LVEF  $\leq 40\%$  prior to the procedure (mean  $32 \pm 6\%$ ) and MR grade 3 or 4 (17.3% and 82.7% respectively). Median LVGLS was  $-8.4\%$  (IQ:  $-6.2\%$  to  $-11.3\%$ ). The mean end-diastolic left ventricle diameter (EDLVD) was  $64 \pm 8$  mm and the mean end-systolic left ventricle diameter (ESLVD),  $48 \pm 11$  mm. As expected, patients in groups 2 and 4 presented larger left ventricular end-diastolic and end-systolic volumes and diameters than those from groups 1 and 3. Most MR was purely functional (71.7%) while in 17.3 % the mechanism of the MR was deemed to be mixed with non-significant differences between groups. Other echocardiographic characteristics of the mitral valve status such as the effective regurgitant orifice area (EROA), the presence of calcification, posterior leaflet retraction, or the location and number of jets were evenly distributed among groups.

Table 2. Basal echocardiographic characteristics.

|                  | Overall  | Group 1 n = 55 | Group 2 n = 31 | Group 3 n = 41 | Group 4 n = 46 | p      |
|------------------|----------|----------------|----------------|----------------|----------------|--------|
| LVEF (%)         | 32 ± 6   | 37 ± 3         | 25 ± 4         | 36 ± 2         | 25 ± 5         | <0.000 |
| EDLVV (mL)       | 193 ± 65 | 163 ± 47       | 278 ± 64       | 183 ± 59       | 203 ± 67       | 0.018  |
| ESLVV (mL)       | 127 ± 53 | 95 ± 35        | 194 ± 56       | 117 ± 42       | 147 ± 55       | 0.004  |
| EDLVD (mm)       | 64 ± 8   | 61 ± 8         | 67 ± 8         | 61 ± 7         | 67 ± 9         | <0.000 |
| ESLVD (mm)       | 48 ± 11  | 43 ± 9         | 58 ± 6         | 47 ± 10        | 55 ± 10        | 0.000  |
| MR Grade (%)     |          |                |                |                |                | 0.096  |
| ≤2               | 0        | 0.0            | 0.0            | 0.0            | 0.0            |        |
| 3                | 17.3     | 20.0           | 19.4           | 24.4           | 6.5            |        |
| 4                | 82.7     | 80.0           | 80.7           | 75.6           | 93.5           |        |
| MR mechanism (%) |          |                |                |                |                | 0.075  |
| Primary          | 4        | 9.1            | 0.0            | 4.9            | 0.0            |        |
| Secondary        | 71.7     | 63.5           | 64.5           | 70.7           | 84.8           |        |
| Mixed            | 24.3     | 25.5           | 35.5           | 24.4           | 15.2           |        |

Table 2. Cont.

|                                            | Overall        | Group 1 n = 55 | Group 2 n = 31  | Group 3 n = 41 | Group 4 n = 46 | p      |
|--------------------------------------------|----------------|----------------|-----------------|----------------|----------------|--------|
| Mitral annulus calcification (%)           | 26.6           | 32.7           | 19.4            | 32.5           | 17.4           | 0.401  |
| Subvalvular apparatus calcification (%)    | 8.2            | 5.7            | 3.7             | 5.6            | 16.7           | 0.139  |
| Posterior leaflet retraction (%)           |                | 61.8           | 61.3            | 57.5           | 56.5           | 0.941  |
| Excentric jet (%)                          | 17.4           | 27.3           | 19.4            | 7.5            | 13.0           | 0.068  |
| Multiple jets (%)                          | 10.7           | 14.6           | 3.5             | 0.0            | 19.6           | 0.012  |
| EROA (cm)                                  | 0.4 ± 0.2      | 0.4 ± 0.2      | 0.4 ± 0.1       | 0.5 ± 0.2      | 0.4 ± 0.2      | 0.187  |
| Mitral Mean Gradient (mmHg)                | 1.5 ± 0.6      | 1.7 ± 0.8      | 1.5 ± 0.7       | 1.5 ± 0.6      | 1.3 ± 0.4      | 0.474  |
| Mitral Valvular Area (cm <sup>2</sup> )    | 5.7 ± 1.4      | 5.8 ± 1.3      | 5.4 ± 1.6       | 5.6 ± 1.3      | 5.9 ± 1.9      | 0.874  |
| Systolic Pulmonary Artery Pressure (mmHg)  | 48 ± 15        | 48 ± 13        | 44 ± 15         | 51 ± 17        | 46 ± 14        | 0.250  |
| LVGLS (%)                                  | 8.4 (6.2–11.3) | 11.3 (10–12.8) | 11.4 (9.6–12.3) | 5.7 (5–6.8)    | 6.9 (5–7.7)    | <0.000 |
| Tricuspid regurgitation grade (%)          |                |                |                 |                |                | 0.197  |
| 0–1                                        | 52             | 64.0           | 40.0            | 50.0           | 50.0           |        |
| 2                                          | 15.7           | 16.0           | 20.0            | 21.4           | 8.8            |        |
| 3                                          | 19.6           | 4.0            | 33.3            | 17.9           | 26.5           |        |
| 4                                          | 12.8           | 16.0           | 6.7             | 10.7           | 14.7           |        |
| TAPSE (mm)                                 | 17 ± 4         | 18 ± 4         | 18 ± 4          | 17 ± 4         | 16 ± 4         | 0.190  |
| Right Ventricle Fractional Area Change (%) | 40 ± 12        | 38 ± 11        | 40 ± 15         | 43 ± 10        | 40 ± 16        | 0.570  |
| EDRVD (mm)                                 | 47 ± 13        | 50 ± 13        | 51 ± 15         | 42 ± 8         | 46 ± 17        | 0.040  |
| LAV (mL)                                   | 106 ± 55       | 118 ± 41       | 104 ± 39        | 104 ± 43       | 96 ± 29        | 0.258  |

LVEF: left ventricular ejection fraction; EDLVV: end-diastolic left ventricular volume; ESLVV: end-systolic left ventricular volume; EDLVD: end-diastolic left ventricular diameter; ESLVD: end-systolic left ventricular volume; EROA: effective regurgitant orifice area; LVGLS: left ventricular global longitudinal strain; EDRVD: End-diastolic right ventricular diameter; LAV: left atrium volume.

Right ventricular function assessed by TAPSE (tricuspid annular plane systolic excursion) was slightly more impaired in groups 3 and 4 in comparison with groups 1 and 2 ( $17 \pm 4$  mm and  $16 \pm 4$  mm vs.  $18 \pm 4$  mm, respectively,  $p = 0.011$ ) even though there were no differences in the fractional area change. Right ventricular, diameter was larger in groups 1 and 2 ( $50 \pm 13$  and  $51 \pm 15$  mm) than in patients of groups 3 and 4 ( $42 \pm 8$  and  $46 \pm 17$  mm,  $p = 0.040$ ).

### 3.2. Procedural Results

The procedure was highly successful in all subgroups with an overall procedural success rate of 96.5%. Two-thirds of the clips implanted were first and second generation and 33% of the clips implanted were third-generation. Procedural complications were infrequent and mostly related to vascular access bleeding (Table 3). One patient died in the first 24 h due to heart failure and two patients presented with a stroke during the first 24 h post-procedure.

**Table 3.** Procedural outcomes.

|                                      | Overall   | Group 1 <i>n</i> = 55 | Group 2 <i>n</i> = 31 | Group 3 <i>n</i> = 41 | Group 4 <i>n</i> = 46 | <i>p</i> |
|--------------------------------------|-----------|-----------------------|-----------------------|-----------------------|-----------------------|----------|
| Technical success (%)                | 99.4      | 98.2                  | 100.0                 | 100.0                 | 100.0                 | 0.540    |
| Procedural success (%)               | 96.5      | 96.4                  | 100.0                 | 100.0                 | 91.3                  | 0.096    |
| Number of Clips placed               |           |                       |                       |                       |                       | 0.834    |
| 1                                    | 64.2      | 67.3                  | 67.7                  | 58.5                  | 63.0                  |          |
| 2                                    | 28.3      | 29.1                  | 25.8                  | 31.7                  | 26.1                  |          |
| 3                                    | 7.5       | 3.6                   | 6.5                   | 9.8                   | 10.9                  |          |
| ≥4                                   | 0         | 0.0                   | 0.0                   | 0.0                   | 0.0                   |          |
| Partial/Complete Detachment (%)      | 1.2       | 0.0                   | 6.4                   | 0.0                   | 0.0                   | 0.073    |
| Embolization (%)                     | 0         | 0.0                   | 0.0                   | 0.0                   | 0.0                   | N/A      |
| Chords Rupture (%)                   | 0.6       | 1.8                   | 0.0                   | 0.0                   | 0.0                   | 0.544    |
| Conversion to surgery (%)            | 0.1       | 0.0                   | 0.0                   | 0.0                   | 0.0                   |          |
| Major bleeding MVARC scale (%)       | 4.6       | 1.8                   | 6.4                   | 9.8                   | 2.2                   | 0.232    |
| Cardiac Tamponade (%)                | 0         | 0.0                   | 0.0                   | 0.0                   | 0.0                   | N/A      |
| Residual MR (%)                      |           |                       |                       |                       |                       | 0.282    |
| 0                                    | 2.3       | 1.8                   | 0.0                   | 7.3                   | 0.0                   |          |
| 1                                    | 50.3      | 54.6                  | 51.6                  | 48.8                  | 45.7                  |          |
| 2                                    | 42.8      | 36.4                  | 48.4                  | 43.9                  | 45.7                  |          |
| 3                                    | 2.9       | 3.6                   | 0.0                   | 0.0                   | 6.5                   |          |
| 4                                    | 1.7       | 3.6                   | 0.0                   | 0.0                   | 2.2                   |          |
| Residual Mitral Mean Gradient (mmHg) | 2.8 (2–4) |                       |                       |                       |                       |          |
| Stroke (%)                           | 1.2       | 1.8                   | 0.0                   | 2.4                   | 0.0                   | 0.636    |
| Peri-operative mortality (<24 h) (%) | 0.6       | 0.0                   | 0.0                   | 0.0                   | 2.2                   | 0.427    |

### 3.3. Follow-Up Results

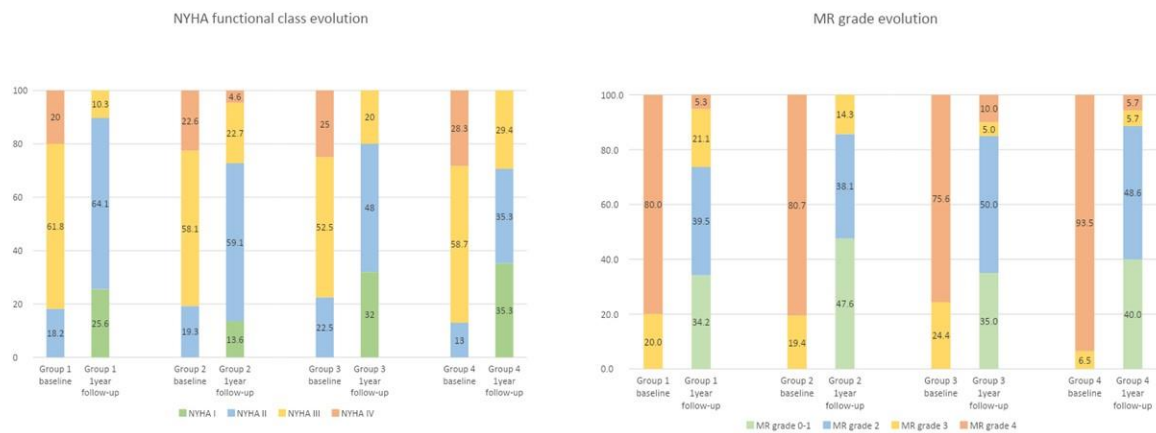
Median follow-up was 711 days (IQR:280–1250 days).

At one-year follow-up, 82.5% of patients remained with MR grade  $\leq 2$  and 79.2% in NYHA functional class  $\leq \text{II}$  (Figure 1). Although the percentage of patients with a maintained MR grade  $\leq 2$  was numerically lower in group 1 than in the rest of the groups, this difference did not reach statistical significance ( $p = 0.425$ ). Twelve-month NYHA class was higher in groups 2 and 4, although it did not reach statistical significance ( $p = 0.135$ ). Throughout the study period, 14% of the patients were admitted to the hospital due to heart failure, translating into a reduction of nearly 80% in re-hospitalizations as compared to the rate of hospitalizations the year before the procedure.

Thirteen patients (7.5%) died during this period due to cardiovascular reasons and two patients (1.18%) received a cardiac transplant. Adjusted Cox model regression survival analysis yielded that a worse value of LVGLS was an independent predictor of cardiovascular mortality in patients with a more altered LVEF (HR: 3.3; 95% CI: 1.1–10,  $p = 0.023$ ) while in those with a more preserved LVEF, LVGLS was not a predictor of cardiovascular mortality (OR:1.1; 95% CI:0.3–3.1;  $p = 0.956$ ), (Table 4). Kaplan–Meier analysis curves illustrate this finding, as shown in Figure 2. However, when evaluating the rate of re-admission due to



heart failure, there were no differences regarding the status of LVGLS in either the patients with a higher LVEF nor those with alower LVEF (Figure 3).

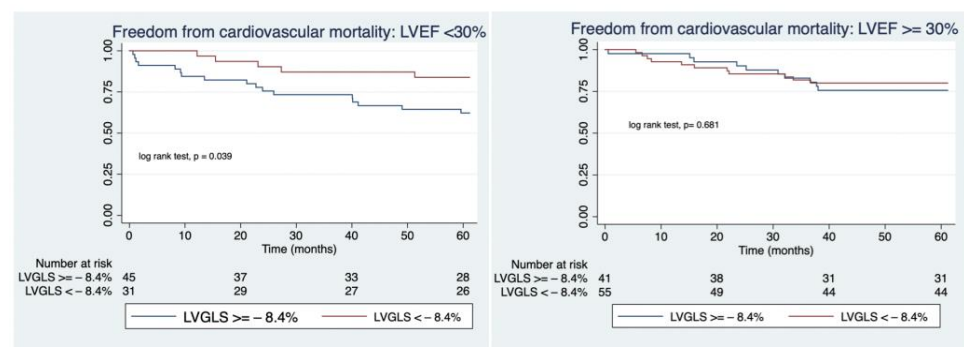


**Figure 1.** NYHA functional class and MR grade evolution (data from baseline and at one-year follow-up) in the different groups.

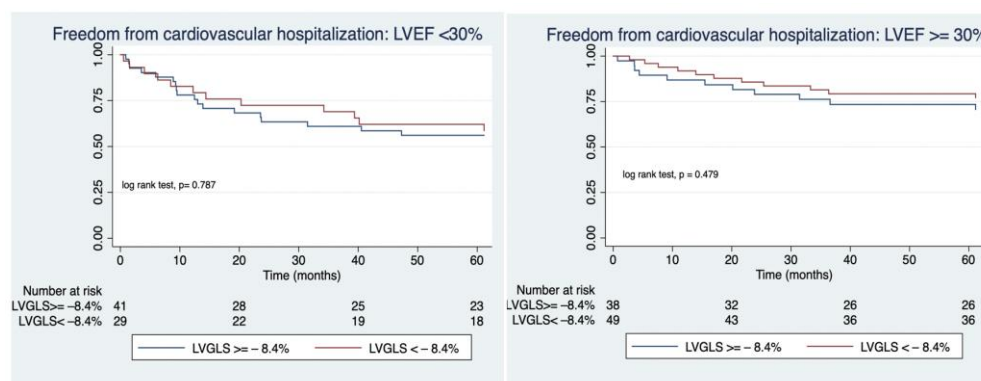
**Table 4.** Adjusted Cox regression analysis for cardiovascular mortality.

| LVEF $\geq$ 30%                           |     |          |         |
|-------------------------------------------|-----|----------|---------|
|                                           | HR  | 95% CI   | p Value |
| Ischemic Cardiomyopathy                   | 2.0 | 0.7–6.2  | 0.211   |
| Glomerular filtrate rate < 60             | 2.3 | 0.9–5.9  | 0.880   |
| Previous Year Heart Failure Admission (%) | 0.7 | 0.2–1.9  | 0.442   |
| LVGLS                                     | 1.1 | 0.3–3.1  | 0.956   |
| SPAP                                      | 0.4 | 0.1–1.1  | 0.060   |
| EDRVD                                     | 1.1 | 0.3–3.2  | 0.941   |
| LVEF < 30%                                |     |          |         |
|                                           | HR  | 95% CI   | p value |
| Ischemic Cardiomyopathy                   | 1.7 | 0.6–4.4  | 0.288   |
| Glomerular filtrate rate < 60             | 1.4 | 0.5–3.6  | 0.502   |
| Previous Year Heart Failure Admission (%) | 1.4 | 0.4–5.3  | 0.599   |
| LVGLS                                     | 3.3 | 1.4–10   | 0.023   |
| SPAP                                      | 0.9 | 0.4–2.4  | 0.856   |
| EDRVD                                     | 2.8 | 0.8–10.6 | 0.134   |

LVGLS: Left ventricular global longitudinal strain; SPAP: systolic pulmonary artery pressure; EDRVD: End diastolic right ventricular diameter.



**Figure 2.** Kaplan–Meier freedom from cardiovascular mortality.



**Figure 3.** Kaplan-meier freedom from re-hospitalization due to heart failure.

#### 4. Discussion

The main findings of this study are: (1) M-TEER with the MitraClip system is safe even in the presence of left ventricle dysfunction; (2) the procedure is effective and its mid-term durability is high; and (3) left ventricular global longitudinal strain provides valuable prognostic information, especially in patients with a more impaired left ventricular ejection fraction.

Nowadays, MitraClip has proven to be a relatively safe therapy with high procedural effectiveness when applied to selected patients in high-volume centers [6,7,9,10]. Our study shows that this affirmation also applies to selected patients with poor left ventricular performance—measured as those with  $LVEF \leq 40\%$ —in whom the procedure was found to be successful in 97% of cases and in whom we found out a very low peri-procedural mortality rate (0.6%) as well as a low complication rate that was mainly driven by vascular access bleeding (4.6%). However, it should be noted that all patients had been previously evaluated by the local heart team ensuring not only a technical plausibility of the repair but also pre-procedural guideline-directed medical therapy.

Nevertheless, despite its safety, the main concern about this technique in this setting is its mid-term durability and whether the improvement in MR grade is translated into an improvement in quality and expectancy of life. While several reports have pointed out that M-TEER could be safe and effective regardless of LVEF [23] others have published different results that may indicate that the treatment may be futile if advanced left ventricular dysfunction is already present [9,24–27]. These controversial results have directed the focus of attention toward the pre-selection of patients and currently, efforts are being made in order to define the optimal candidates for this therapy. In this way, the analysis of myocardial deformation with the evaluation of global longitudinal strain of the left ventricle (LVGLS) could be of interest as it has already been proven that this tool enables more precise examination of the cardiac muscle performance. Furthermore, LVGLS could also provide with valuable information as it has been found to be a good predictor of mortality in patients with reduced LVEF [18] as well as of left ventricular remodeling six months after repair with MitraClip [27,28].

In our cohort, the reduction in MR grade was highly sustained over time as more than 80% of the patients maintained a mild regurgitation (MR grade I or II) at one-year of follow-up. More importantly, at that time nearly 80% of the patients were at NYHA class I or II which is a substantial improvement in quality of life since more than 82% of patients were at NYHA class III or IV prior to the procedure, being that result in line with previous studies [5,6,10]. Of note, the percentage of rehospitalizations due to cardiac failure within the first year of follow-up decreased significantly in comparison with the rate of heart failure-related admissions the year prior to the repair (14% vs. 82%, respectively). This reduction was observed both in the group with a more diminished LVEF as well as in the group with a more preserved LVEF regardless of baseline LVGLS as shown in Figure 3. However, when comparing the cardiac mortality at one-year follow-up, we found out that

while those patients with a lower LVEF and a more deteriorated LVGLS had a significantly higher rate of cardiac mortality as compared with those with a less impaired LVGLS, in the subgroup of patients with a baseline LVEF  $\geq 30\%$ , the status of LVGLS was not a predictor of events (Figure 2). It could be argued that LVGLS could be more altered in patients with larger left ventricular diameters and volumes, which already have a poorer prognosis, and therefore, its additional value, could be questionable. In order to examine this concern, we studied the correlations between LVGLS and end-diastolic left ventricular diameter (EDLVD) and end-diastolic left ventricular volume (EDLVV). In our population, LVGLS was not correlated neither with EDLVD or EDLVV ( $\rho = -0.007$ ,  $p = 0.933$  and  $\rho = -0.016$ ,  $p = 0.33$  respectively) which confers the assessment of LVGLS an additional value in terms of prognosis. These findings translate that LVGLS could be an indicator of more advanced deterioration of the cardiac muscle that, even if an amelioration of the volume overload occurs, may not be able to adapt to the new loading condition, especially in severely depressed LVEF cases. Therefore, proper patient assessment, including the evaluation of myocardial deformation using LVGLS, could lead to the recognition of patients who may benefit the most and it could also lead to prompt therapy in those patients with progressive worsening of left ventricular function in terms of progressive worsening of LVGLS. However, larger and randomized trials are needed to fully examine the benefits of this approach.

There are several limitations to be considered in this paper. The first one is its own nature as an observational and retrospective study with a lack of a control group to compare outcomes.

Second, during the period of study, the European Society of Cardiology's recommendations in terms of oral treatment for heart failure changed according to new data available and thus, patients included at the beginning of the study were under different medication than the ones included later [29–31].

Third, the lack of core-lab adjudication of echocardiographic parameters could be considered a limitation. However, it reflects a real-world situation in which a local expert in cardiac imaging performs the acquisition and evaluation of the baseline echocardiograms as well as monitors the procedure and post-procedural echocardiograms. Moreover, the software used to calculate LVGLS was automatic requiring minimal adjustments to optimized automated speckle tracking, thus, reducing interobserver and interinstitutional variability. Despite this, in order to assess interobserver variability, 17 patients were randomly selected and the LVGLS was assessed by two different observers obtaining a kappa index of 0.946,  $p < 0.001$ .

Fourth, the availability of the required images for the analysis of the baseline myocardial strain is not high in our cohort (63% of the initial population) and it could have caused a selection bias as a pure secondary cause of MR was more frequently found in patients without LVGLS availability than in those with LVGLS availability (Supplemental Tables S1 and S2).

Last, two different softwares for the analysis of LVGLS were used as per availability in the participating centers. Since there has been reported an inter-vendor variability in the values of LVGLS, care should be taken in interpreting a specific cut-off point or value.

## 5. Conclusions

Transcatheter edge-to-edge mitral repair with the MitraClip system is safe and it improves the mid-term quality of life of patients regardless of LVEF. Myocardial deformation evaluated by means of LVGLS can help in the selection of optimal candidates and timing for this procedure, as well as to recognize those patients with worse prognoses.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/jcm12124116/s1>, Table S1: Baseline clinical characteristics in patients with LVGLS available and those with no LVGLS available; Table S2. Baseline clinical characteristics in patients with LVGLS available and those with no LVGLS available; Figure S1. Example of analysis of left global longitudinal strain being measured.

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## **5.RESUMEN GLOBAL DE LOS RESULTADOS**





### 5.1. Reparación percutánea borde-a-borde en presencia de MAC

Para este primer artículo se incluyeron un total de 852 pacientes consecutivos tratados con RPBB en siete centros con alta experiencia en dicho procedimiento. Se estableció el grado de MAC a partir de la ETE previa al procedimiento considerándose MAC ligero si se limitaba a un tercio del anillo mitral; moderado, si incluía de uno a dos tercios del anillo; y severo si comprometía a todo el anillo o si presentaba un grosor mayor a 4mm (131,143). De ellos, el 30% presentaban algún grado de MAC siendo moderado o severo en el 5.5% y 2.5% de los pacientes respectivamente. Aquellos pacientes con MAC moderado o severo eran ligeramente mayores (78.3 vs 72.8 años,  $p=0.001$ ) y se encontraban en clase funcional NYHA más avanzada (el 95% se encontraban en NYHA 3 o 4 vs el 85%,  $p=0.037$ ) respecto al resto de la población. Anatómicamente, los pacientes de este grupo exhibían características más complejas como la presencia de calcificación del aparato subvalvular (35.6% vs 4.9%,  $p<0.001$ ), jets excéntricos (54.1% vs 31.3%,  $p<0.001$ ) o mayor gradiente transvalvular basal (2.3mmHg vs 1.7mmHg,  $p<0.001$ ) comparado con el resto de pacientes.

El éxito del procedimiento fue alto en este subgrupo (95.1%) si bien hubo un porcentaje más alto de pacientes con gradiente transvalvular mayor a 5mmHg (18.5% vs 5%,  $p=0.001$ ) tras la intervención. El procedimiento transcurrió sin complicaciones en la mayoría de los casos si bien en 2 pacientes con MAC moderado o severo y en 5 pacientes sin ella, fue necesaria la reconversión a cirugía durante el ingreso y se reportaron un fallecimiento en la cohorte de MAC moderado o severo y 6 en el resto de la población.

Durante el seguimiento a un año la mayoría de pacientes mantenían un grado de IM residual  $\leq 2$  (90.6% de la cohorte con MAC y 79.5% del resto,  $p=0.129$ ) y clase

funcional NYHA  $\leq 2$  (80.5% vs 78.5%,  $p=0.453$ ). Además, se observó una reducción en la tasa de rehospitalizaciones por insuficiencia cardíaca en hasta el 78% y 65% en pacientes con MAC y en el resto de la población respectivamente. Ningún paciente de la cohorte con MAC moderado o severo precisó reintervención mitral. La mortalidad cardiovascular a un año fue similar en los dos grupos si bien el grupo con MAC moderado o severo presentó mayor mortalidad por cualquier causa (19.7% vs 11.3%,  $p=0.050$ ).

## **5.2. Reparación borde-a-borde en presencia de FEVI deprimida.**

En el segundo artículo de este compendio, se incluyeron un total de 172 pacientes con IM severa sintomática y FEVI  $\leq 40\%$  tratados con RPBB en 5 centros españoles. Todos ellos disponían de análisis previo al procedimiento de SGLVI. Este análisis se realizó por expertos locales en imagen cardiovascular con dos tipos de software distintos: el QLAB Advanced Quantification Software 13.0 Koninklijke Philips Electronics NV 2019 y el General Electric Automated Function Imaging Software. Ambos trazaban automáticamente los bordes endocárdicos al final de la sístole y realizaban el análisis de SGLVI de forma automática. Posteriormente se dividió la muestra en 4 cohortes de acuerdo a las medianas de la FEVI y SGLVI: el grupo 1 lo conformaban pacientes con FEVI  $\geq 30\%$  y LVGLS  $< -8.4\%$ ; el grupo 2, pacientes con FEVI  $< 30\%$  y LVGLS  $< -8.4\%$ ; el grupo 3, pacientes con FEVI  $\geq 30\%$  y SGLVI  $\geq -8.4\%$ ; y el grupo 4, pacientes con FEVI  $< 30\%$  y SGLVI  $\geq -8.4\%$ .

No se encontraron diferencias en las características clínicas y demográficas pre-procedimiento en los cuatro grupos. No obstante, a nivel ecocardiográfico, los grupos 2 y 4 presentaron mayores diámetros y volúmenes de VI que los grupos 1 y 3.

El procedimiento fue exitoso en el 96.5% de los casos, con una baja tasa de complicaciones que fueron derivadas principalmente de sangrado del acceso vascular. Un paciente falleció en las primeras 24 horas debido a insuficiencia cardíaca refractaria y 2 pacientes presentaron un ictus en ese periodo.

A un año, el 82.5% de los pacientes mantenían un grado de IM residual  $\leq 2$  y un 79.2% permanecían en clase funcional NYHA  $\leq 2$  sin encontrar diferencias significativas entre grupos ( $p=0.425$  y  $p=0.135$  respectivamente). Además, la tasa de rehospitalizaciones por insuficiencia cardíaca se disminuyó en un 80%.

En cuanto al análisis del SGLVI, éste se mostró predictor de mortalidad cardiovascular en aquellos pacientes con FEVI  $<30\%$  (HR:3.3;95% CI:1.1-10,  $p=0.023$ ) y no en aquellos con FEVI  $\geq 30\%$ .



## **6.RESUMEN GLOBAL DE LA DISCUSIÓN**



Durante la realización de esta tesis doctoral hemos intentado caracterizar aquellos pacientes que podrían ser candidatos óptimos para RPBB, prestando especial interés a dos poblaciones específicas: aquellos con calcificación de anillo mitral (MAC) y aquellos con FEVI deprimida.

### **6.1. Reparación percutánea borde-a-borde en presencia de MAC**

Como se ha comentado previamente en la introducción, la prevalencia de MAC en la población afecta de IM es alta, rondando casi el 30% en algunas series. No obstante, a pesar de su alta prevalencia, su tratamiento quirúrgico supone aún un reto por su complejidad técnica y por la alta comorbilidad asociada, lo que conlleva resultados clínicos subóptimos (48,132–136,138,139). Por este motivo, la posibilidad de reparación mediante una técnica menos invasiva podría suponer una mejora en el tratamiento de estos pacientes.

Nuestro trabajo demuestra que, en población seleccionada y en centros con experiencia en RPBB, ésta podría considerarse una alternativa segura y eficaz para el tratamiento de la IM en presencia de MAC. Observamos una alta tasa de eficacia del procedimiento a pesar de presentar inicialmente anatomías más complejas, como previamente especificado, con un buen perfil de seguridad: tan sólo en 5 de los 61 pacientes con MAC moderado o severo de nuestra población no se consiguió reducir el grado de IM a  $\leq 2$ , precisando dos de ellos cirugía urgente por IM masiva tras desgarro del velo posterior. Estos últimos dos pacientes presentaban MAC moderado sin extensión a aparato subvalvular ni a velos y presentaban una longitud de velo posterior aceptable sin restricción del mismo.

Además, durante el seguimiento, la durabilidad de la reparación fue similar en ambos grupos y no se requirió ninguna reintervención en el grupo a evaluar contrastando con los resultados previamente obtenidos en este escenario con la técnica quirúrgica donde la durabilidad era reducida y estaba ligada a una mayor necesidad de reintervención además de mayores gradientes transvalvulares (48). No obstante, sí que observamos que los pacientes con MAC moderado o severo presentaban mayor gradiente transvalvular residual (18.5% de los pacientes presentaron un gradiente transvalvular mayor a 5mmHG) si bien éste no se relacionó con un incremento de eventos cardiovasculares o mortalidad, en línea con lo observado en algunos estudios previos (144,145).

Cabe destacar que, además de mantener una alta durabilidad desde el punto de vista ecocardiográfico, los resultados clínicos a un año también fueron positivos: el 80% de los pacientes con MAC se encontraban en clase funcional NYHA 1 o 2 y se redujo las hospitalizaciones por insuficiencia cardíaca en un 78%. Asimismo, la mortalidad cardiovascular fue comparable a la de aquellos pacientes sin MAC o con MAC ligero si bien la mortalidad global fue mayor en la cohorte con MAC moderado o severo. Sin embargo, este grupo de pacientes eran más longevos y presentaban mayor comorbilidad, encontrando una correlación marginal entre la mortalidad global y la presencia de MAC en nuestra serie que podría explicar estos hallazgos.

Tras estos resultados, se abre un escenario esperanzador para este tipo de población clásicamente excluida en los estudios aleatorizados, si bien se ha de enfatizar que los procedimientos se llevaron a cabo en centros con alta experiencia y tras un análisis exhaustivo ecocardiográfico que excluía la presencia de calcificación severa en los márgenes libres de los velos o zona de captura del dispositivo lo que lo prohibitivo por alto riesgo de desgarro valvar.



## 6.2. Reparación borde-a-borde en presencia de FEVI deprimida.

Tras la publicación simultánea de los resultados dispares de los estudios MITRAFR y COAPT se generó una controversia en torno al tratamiento con RPBB de pacientes con FEVI reducida, hipotetizándose que, en algunos casos, la función ventricular podía estar ya demasiado dañada y que esta terapia no añadiría beneficio clínico (75). En este sentido, en un primer análisis realizado con la población del Registro Español de MitraClip (**Anexo 1**), observamos que, si bien la terapia mejoraba la clase funcional NYHA de los pacientes independientemente de la FEVI basal, aquellos con FEVI <30% no obtenían el mismo beneficio en términos de mortalidad de cualquier causa o rehospitalización de causa cardiovascular al compararlos con el resto. No obstante, otros estudios posteriores pondrían en entredicho estos hallazgos, al observar mejora sintomática en pacientes incluso con FEVI <30% (104,109). Todos los anteriores tenían en común que caracterizaban la función ventricular a través de la estimación de la FEVI, que podría resultar subóptima en estos pacientes, siendo necesario un método más preciso como podría ser el análisis del strain o deformación miocárdica ventricular (SGLVI), parámetro que no se encuentra tan afectado por las condiciones de precarga y precarga (140,141,146–148). Además, al utilizar softwares automáticos, la variabilidad intra e inter observador puede encontrarse disminuida. De hecho, para el segundo estudio de este compendio, analizamos la variabilidad inter-observador seleccionando de manera aleatorizada 17 pacientes cuyo SGLVI fue analizado por dos diferentes operadores obteniendo un índice kappa de 0.946 ( $p<0.001$ ). Al añadir este parámetro a nuestra cohorte en el segundo artículo de este compendio, observamos que, si bien la RPBB es segura y duradera en términos de reducción de la IM y mejora de la clase funcional NYHA incluso en FEVI deprimida, en aquellos casos en los que la FEVI se

encuentra más alterada ( $FEVI < 30\%$ ), el análisis del SGLVI ayuda a discernir qué pacientes presentarían peor pronóstico al presentar un grado de disfunción más avanzado. Del mismo modo, a pesar de que la FEVI pueda estar severamente deprimida, aquellos pacientes con SGLVI aún preservado o no tan afectado, podrían encontrarse aún en situación favorable para el tratamiento con RPBB mostrando no sólo mejoría sintomática sino también en cuanto a supervivencia. Este hallazgo podría explicar, en parte, los diferentes resultados obtenidos en distintos estudios: mientras algunos grupos proclaman la efectividad de la RPBB aún en presencia de FEVI severamente deprimida (104,109), otros sostienen que el tratamiento podría ser no tan beneficioso e incluso fútil en estos pacientes (55,106,149). Así, la evaluación del SGLVI ayuda a reconocer a aquellos pacientes que aún pueden beneficiarse de la terapia y a determinar una actuación precoz en presencia de deterioro progresivo del SGLVI.

### **6.3. Reparación percutánea borde-a-borde en poblaciones especiales**

Dentro del grupo de pacientes con FEVI deprimida, existe un grupo particular comprendido por sujetos relativamente jóvenes, en clase funcional avanzada y con IM severa que se encuentran por este motivo en lista de espera de trasplante cardíaco o en espera de ser poder ser considerados candidatos aptos para ello. En el registro MitraBridge (**Anexos 2 y 3**) se evaluó el tratamiento con RPBB como puente a trasplante en una muestra de hasta 153 pacientes con estas características observando una mejora sintomática significativa que permitió, en casi una cuarta parte de los pacientes tratados, la salida de lista de espera al mejorar su estado funcional y, en 13.5% de los pacientes no candidatos inicialmente a trasplante, su incorporación a ésta.

Existe otro subgrupo de pacientes con características propias tales como aquellos que presentan IM aguda a consecuencia de un infarto agudo de miocardio. Estos pacientes, por lo general, presentan un riesgo muy elevado de mortalidad quirúrgica y, por tanto, una terapia menos invasiva (como la RPBB) podría ser una opción más segura. En el **Anexo 4** se evaluó esta estrategia de forma retrospectiva en 471 pacientes en los que se comparó la estrategia de manejo conservador, la cirugía cardíaca y la RPBB en pacientes con IM isquémica aguda excluyendo aquellos casos secundarios a ruptura papilar. En ellos, se observó una mayor supervivencia en el grupo tratado con RPBB siendo el pronóstico peor en aquellos casos que se manejaron de forma conservadora a pesar de ser inicialmente los que mejor estado funcional presentaban. Así, una estrategia de tratamiento invasivo precoz, especialmente con RPBB, podría mejorar la supervivencia de estos pacientes. Incluso, en una serie más reducida de pacientes con IM aguda isquémica en la que se comparó la efectividad de la RPBB en pacientes con shock cardiogénico vs aquellos en situación hemodinámica más favorable (**Anexo 5**), la RPBB demostró ser un tratamiento altamente efectivo en la reducción del grado de IM y mejora de clase funcional NYHA con tasas de mortalidad y rehospitalización similares en ambos grupos en el seguimiento a 7 meses. Siguiendo esta línea de investigación, en el **Anexo 6** se evaluó de forma retrospectiva a 105 pacientes con IM aguda isquémica y disfunción ventricular a causa del infarto, tratados con RPBB, sin observar diferencias en reducción del grado de IM, tasa a corto plazo de rehospitalizaciones o mortalidad a un año en pacientes con disfunción ventricular severa o sin ella.

#### **6.4. Otros parámetros a evaluar en la selección de candidatos a reparación percutánea borde-a-borde**

De acuerdo a los objetivos planteados, se intentaron definir otras variables anatómicas y clínicas diferentes a las clásicamente conocidas, que pudieran ayudar a perfilar al candidato óptimo para la RPBB. Entre los estudios destinados a este fin, en el **Anexo 7** se valoró la capacidad predictora de la ratio TAPSE/PASP como subrogada del acoplamiento de ventrículo derecho a arteria pulmonar y, por tanto, de función ventricular derecha (150). En él se observó, en una muestra de 228 pacientes tratados con RPBB, cómo dicho ratio podía servir como predictor de mortalidad de cualquier causa y de rehospitalización por insuficiencia cardíaca tras la terapia reproduciendo los resultados previamente publicados del registro europeo (151). Del mismo modo, otro factor que podría aumentar al riesgo de mortalidad y rehospitalización por insuficiencia cardíaca fue el estado nutricional previo a la intervención (**Anexo 8**). De forma interesante, este registro mostró cómo la mayoría de pacientes presentan cierto grado de malnutrición previo a la RPBB e incluso una quinta parte presenta malnutrición moderada o severa con el consiguiente aumento del riesgo de mortalidad e insuficiencia cardíaca. La importancia de este hallazgo radica en que su detección temprana y tratamiento previo a la RPBB podría disminuir dicho riesgo y, por tanto, mejorar los resultados a largo plazo de la terapia.

Dentro de la misma línea de trabajo, y dado que los scores de estratificación de riesgo empleados más habitualmente como el EuroScore II (European System for Cardiac Operative Risk Evaluation II) o STS (Society of Thoracic Surgeons) Score no están especialmente diseñados para la evaluación del riesgo en IM, se diseñó un estudio (**Anexo 9**) con el que, a raíz del análisis de la población estudiada en el Anexo 8, se

lograron identificar hasta 8 factores predictores de mortalidad a 2 años. Dichos factores fueron la edad  $\geq 75$  años, la presencia de anemia, un filtrado glomerular inferior a 60 mL/min/1.73m<sup>2</sup>, FEVI <40%, la presencia de vasculopatía periférica, EPOC, la necesidad previa de altas dosis de furosemida y la ausencia de inhibidores del sistema renina-angiotensina en su tratamiento habitual. Se determinó el “MitraScore” asignando un punto a cada uno de estos factores independientes de mortalidad que incrementaban el riesgo relativo de ésta en un 55% (HR:1.55;95% CI:1.44-1.67;  $p < 0.001$ ). Este score fue posteriormente validado externamente en la población del registro GIOTTO mostrando correlación además con la tasa de rehospitalización por fallo cardíaco y con la probabilidad de mejora clínica tras la RPBB.

## **6.5. Limitaciones**

Deben de tenerse en cuenta varias consideraciones al interpretar los resultados de esta tesis doctoral:

1. El carácter retrospectivo del análisis de las poblaciones implicadas que representa la limitación principal a este estudio.
2. La ausencia de un laboratorio de ecocardiografía central y ciego y el hecho de que se emplearon dos marcas comerciales distintas para el análisis del SGLVI lo que podría suponer una limitación (152). No obstante, esto refleja una situación más cercana a la práctica clínica habitual donde además se usaron softwares automáticos por lo que la variabilidad inter e intra observador se minimiza, si bien se debe ser cuidadoso en la interpretación del punto de corte empleado.
3. Durante el periodo del estudio, las recomendaciones en cuanto a tratamiento oral para el manejo de la insuficiencia cardíaca se fueron modificando de acuerdo a

la evidencia científica por lo que los pacientes incluidos se encontraban  
basalmente bajo distinto tratamiento médico.

4. La terapia de RPBB fue llevada a cabo en centros seleccionados con una alta experiencia en este tipo de procedimientos y, por tanto, los resultados no son generalizables a centros que inician esta terapia.

## **7.CONCLUSIONES**





- La reparación percutánea borde-a-borde (RPBB) mitral es una técnica segura en pacientes con calcificación del anillo mitral, siempre que se realice en centros con una amplia experiencia y tras haber excluido la extensión del calcio a las zonas de captura de los velos.
- La RPBB demuestra ser eficaz en la reducción del grado de IM y mejora los síntomas, así como disminuye la tasa de hospitalizaciones por insuficiencia cardíaca en pacientes con calcificación del anillo mitral.
- En pacientes con FEVI deprimida, la RPBB se muestra segura y eficaz, mejorando el grado de IM, la clase funcional NYHA y disminuyendo la tasa de hospitalización por insuficiencia cardíaca en el seguimiento.
- El análisis del strain global longitudinal de ventrículo izquierdo (SGLVI) emerge como una herramienta valiosa, principalmente en pacientes con FEVI severamente deprimida, para determinar el momento y la selección adecuada de pacientes para la RPBB.



## **8. PERSPECTIVAS FUTURAS**



La terapia de RPBB ha demostrado su seguridad y versatilidad en los distintos escenarios abordados en esta tesis. En la actualidad, se ha consolidado como una alternativa segura y eficaz a la cirugía para reducir el grado de IM, tanto en casos de IMF como en casos de IMD de alto riesgo quirúrgico.

Sin embargo, en el caso de la IMF, la traducción clínica y el pronóstico de esta intervención parecen estar ligados al momento en que se lleva a cabo dentro de la evolución de la enfermedad cardíaca subyacente, así como al tratamiento médico coadyuvante. En ese sentido, cobra especial relevancia la monitorización continua de la enfermedad de base y la posibilidad de intervenir de manera temprana en caso de detectar un deterioro incipiente de la función ventricular o un empeoramiento de los síntomas y la clase funcional. Sería interesante, en el futuro, realizar estudios dirigidos a evaluar la estrategia de monitorización de la función ventricular mediante la estimación continuada del SGLVI y su impacto en el momento de la intervención y en la evolución clínica posterior.

Por otro lado, en el ámbito de la IM primaria o degenerativa, actualmente la atención se centra en determinar el papel de la RPBB en casos de menor riesgo quirúrgico y en situaciones de mayor complejidad anatómica. Están en marcha en esa línea de investigación los estudios aleatorizados REPAIR MR (Percutaneous MitraClip Device or Surgical Mitral Valve Repair in Patients with Primary Mitral Regurgitation who are Candidates for Surgery, ClinicalTrials.gov: NCT04198870), PRIMARY (Percutaneous or Surgical Mitral Valve Repair, ClinicalTrials.gov: NCT05051033) y MITRA-HR (Multicenter Study of MitraClip Transcatheter Mitral Valve Repair in Patients with Severe Primary Mitral Regurgitation Eligible for High-Risk Surgery, ClinicalTrials.gov: NCT03271762) de los que se esperan resultados en los próximos años y que comparan la estrategia de RPBB versus reparación quirúrgica en pacientes no sólo de alto riesgo

sino también de bajo riesgo quirúrgico. Tras su evaluación, se espera obtener información adicional sobre la factibilidad y la durabilidad de la reparación en este contexto.

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## 10. ANEXOS



## 10.1. Anexo 1

Transcatheter mitral repair for functional mitral regurgitation according to left ventricular function: a real-life propensity-score matched study.

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Article

# Transcatheter Mitral Repair for Functional Mitral Regurgitation According to Left Ventricular Function: A Real-Life Propensity-Score Matched Study

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**Abstract:** Background: Transcatheter mitral valve repair (TMVR) could improve survival in functional mitral regurgitation (FMR), but it is necessary to consider the influence of left ventricular ejection fraction (LVEF). Therefore, we compare the outcomes after TMVR with Mitraclip® between two groups according to LVEF. Methods: In an observational registry study, we compared the outcomes in patients with FMR who underwent TMVR with and without LVEF <30%. The primary endpoint was the combined one-year all-cause mortality and unplanned hospital readmissions due to HF. The secondary end-points were New York Heart Association (NYHA) functional class and mitral regurgitation (MR) severity. Propensity-score matching was used to create two groups with the same baseline characteristics, except for baseline LVEF. Results: Among 535 FMR eligible patients, 144 patients with LVEF <30% (group 1) and 144 with LVEF ≥30% (group 2) had similar propensity scores and were included in the analyses. The primary study endpoint was significantly higher in group 1 (33.3% vs. 9.4%,  $p = 0.002$ ). There was a maintained improvement in secondary endpoints without significant differences among groups. Conclusion: FMR patients with LVEF <30% treated with MitraClip® had higher mortality and readmissions than patients with LVEF ≥30% treated with the same device. However, both groups improved the NYHA functional class and MR severity.

**Keywords:** Mitraclip; functional mitral regurgitation; transcatheter; left ventricular ejection Fraction

## 1. Introduction

Mitral regurgitation (MR) has become the most common valvular disease. In fact, up to 1 in every 10 individuals aged 75 years or older present moderate or severe MR [1]. The etiology of MR can be either degenerative or functional. Unlike degenerative MR (DMR), in functional mitral regurgitation (FMR) the components of the mitral apparatus are preserved. Thus, FMR is defined as the mitral insufficiency with a lack of leaflet coaptation due to annular dilatation or left ventricular (LV) remodeling [2,3].

In contrast to DMR, where mitral valve surgery can improve the prognosis [4–7], surgical treatment for FMR has not shown to improve functional status or survival [8,9]. Therefore, invasive treatment (either surgical or percutaneous) may be considered in those patients with chronic severe FMR that remain symptomatic despite optimal medical management, when revascularization is not indicated [6,7].

Over the past few years, transcatheter mitral “edge to edge” valve repair (TMVR) using MitraClip® (Abbott Vascular, Menlo Park, CA, USA) system has emerged as a safe and effective treatment option for both high-risk DMR and FMR [10–12].

The latest evidence in the treatment of FMR, which classically has had a very poor prognosis and no specific treatment, has placed this entity in the frontline of clinical debates. Whereas the first two randomized control trials for FMR—comparing TMVR plus medical therapy versus medical therapy alone—confirmed a high rate of procedural success, different clinical results in follow-up were found between both studies [13,14]. The patients in both studies have different baseline characteristics. Therefore, finding the key variable that predicts a good result is of the utmost importance [15].

The presence of significant FMR in heart failure patients has been associated with increased morbidity and mortality [16–18]. Although correction through percutaneous repair can improve survival significantly, the greatest controversy remains around the time of the intervention. If it is carried out in very advanced stages of the disease, it may not be effective [13,14,19].

Left ventricular ejection fraction (LVEF) is one of the most powerful classic independent predictors of survival in heart failure, as well as one of the variables on which the indication of treatment for both degenerative and functional mitral insufficiency depends on [6,7,20]. Even though FMR has been considered not only a marker but also an independent risk factor for adverse events, it is necessary to take into account the influence of LVEF in this context [18,21].

The cut-off point, LVEF = 30%, is the limit indicated by the guidelines to predict the outcome after surgical repair. In line with the surgical point of view in the guidelines, (LVEF) below 30% could also modify the outcome in TMVR [6,7].

Therefore, our aim was to analyze the differences in one-year all-cause mortality and unplanned hospital readmissions due to heart failure in a cohort of FMR patients treated by TVMR according to their LVEF.

## 2. Methods

We performed our study using a registry-based analysis involving patients with severe FMR patients who underwent TMVR using MitraClip®.

Data were obtained from the Spanish MitraClip Registry. This registry is a contemporary prospective clinical-practice registry, and it was endorsed by the Interventional Cardiology Association of the Spanish Society of Cardiology and prospectively included consecutive patients treated with MitraClip from 1 June 2012, to 1 March 2020, from 23 Spanish hospitals. The indication for TMVR was established after multidisciplinary team evaluation (Heart Team) in each center.

A specialized centralized database was designed for the prospective and consecutive inclusion of all of the patients' demographic, echocardiographic, procedural, and follow-up variables.

All included patients signed a dedicated informed consent form. This study was approved by the local Ethical Committee (reference 2020/026).

### 2.1. Study Population

For the purpose of this study, we included all patients in the registry with severe FMR treated with TMVR using MitraClip® (Abbott; Menlo Park, CA, USA) [3,6,7].

FMR etiology was defined as the one shows structurally normal leaflets and chordae but an imbalance between the closing and tethering forces in the valve, secondary to alterations in left ventricular geometry. Degenerative and Mixed MR etiologies were excluded [3,6,7].

In all participant centers, patients with moderate-severe or severe (3 to 4+) FMR, symptomatic despite guideline-directed optimal medical therapy, were evaluated by a multidisciplinary Heart Team

(comprising interventional cardiologists, cardiac surgeons, heart failure specialized cardiologists and cardiac imaging specialists) [6,7]. Informed consent for the procedure was obtained from all patients and TMVR was performed with the MitraClip® edge to edge technique as reported elsewhere [22].

To understand the differences in mortality and unplanned hospital readmissions due to heart failure according to their LVEF, the sample was divided into two groups according to LVEF. Group 1 was composed by patients with severely impaired LVEF (LVEF less to 30%) and group 2 by patients with LVEF  $\geq 30\%$ . Both groups were prospectively followed-up. There were no losses in follow-up.

## 2.2. Variable Definitions

Procedural success was defined as the proper implantation of at least one clip and reduction of the severity of the MR to a grade less than or equal to moderate (2+). The severity of MR, not only for the diagnosis but also for the follow-up, was evaluated by experts cardiac imaging specialists, according to the European Society of Cardiology (ESC) guideline criteria [6,7].

Procedural time was defined as the duration from anesthetic induction to the end of the procedure. Device implantation time was calculated from the insertion of the release system until its removal.

Procedure-related bleeding and its severity were defined according to the criteria of the Bleeding Academic Research Consortium (BARC) [23].

Functional class was defined according to the classification of the New York Heart Association (NYHA).

## 2.3. Study Outcomes

The primary endpoints of the study were (1) the combined 1-year all-cause mortality and unplanned hospital readmissions due to HF, (2) 1-year all-cause mortality and (3) unplanned hospital readmissions due to HF.

The secondary end-points were (1) functional class after TMVR and (2) MR severity after 1-year follow up.

## 2.4. Statistical Analysis

Absolute ( $n$ ) and relative (%) frequencies were calculated for qualitative variables. For quantitative variables, Kolmogorov–Smirnov test was used to assess the normality of the variables. Quantitative variables were expressed as mean  $\pm$  standard deviation if normally distributed and as median (interquartile range) if not. The differences in the qualitative variables were calculated as a percentage difference with the Pearson chi-square test; if 20% or more of cells had expected frequencies  $< 5$ , likelihood ratio correction was performed.

Propensity score matching was used to create two groups with the same baseline characteristics. We estimated propensity scores and matched for LVEF groups ( $< 30\%$  or  $\geq 30\%$ ), using nearest-neighbor matching without replacement. The propensity score is a conditional probability of having a particular exposure given a set of baseline measured covariates. Covariates were chosen based on theoretical knowledge: age (stratified by intervals of 10 years:  $< 60$ ; 60–69; 70–79;  $\geq 80$ ), sex, BMI (stratified  $< 25$  kg/m<sup>2</sup>, 25–29.99 kg/m<sup>2</sup>, and  $\geq 30$  kg/m<sup>2</sup>), hypertension, diabetes mellitus and previous ischemic heart disease.

The matching ratios for the order of formation LVEF groups were 1:1. After the matching, both groups were confirmed to be similar in baseline characteristics using mean standardized differences, which has proved to be the best way, since it does not depend on sample size. Then, outcomes were compared among the groups [24,25].

To evaluate one-year mortality and unplanned readmissions for HF between both groups, Kaplan–Meier survival estimator was used. In conjunction with the stratified log-rank test, the median survival and the survival curves were used to compare the event-free survival rates among the groups. Differences in other quantitative variables were compared with the one-way ANOVA (using post-hoc

Bonferroni analysis for multiple comparisons) or the Kruskal–Wallis test according to the distribution of the variable. Differences in other qualitative variables were compared with the Pearson chi-square test.

For data analysis, the SPSS version 23.0 statistical package was used (IBM Corp.; Armonk, New York, NY, USA).

### 3. Results

#### Study Population

During the study period, there were 946 patients included in the registry and available for analysis. We identified 535 patients with FMR who met the inclusion criteria (Figure 1), of whom a total of 396 (74%) were men and 139 (26%) were women. The mean age was  $71.0 \pm 10.8$  years old, with an average BMI of  $27.2 \pm 4.5$  kg/m<sup>2</sup>.

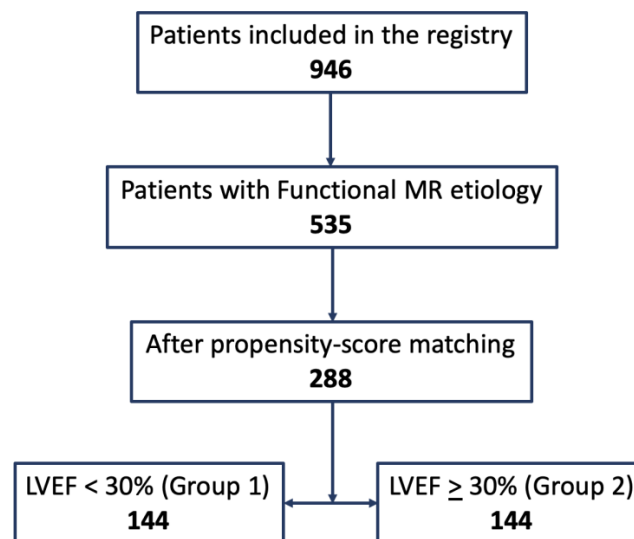


Figure 1. Flow chart of the design of the study.

In the global series, before propensity score matching, there were significant differences between the two groups in several of the baseline variables (Table 1).

**Table 1.** Baseline characteristics in the global series and among both groups according to the left ventricular ejection fraction (LVEF).

| Variable                   | Total FMR Group<br><i>n</i> = 535 | FE < 30%<br><i>n</i> = 229 (42.8%) | FE ≥ 30%<br><i>n</i> = 306 (57.2%) | <i>p</i> |
|----------------------------|-----------------------------------|------------------------------------|------------------------------------|----------|
| Age (years)                | 71.0 ± 10.8                       | 68.1 ± 11.7                        | 73.2 ± 9.7                         | <0.001   |
| Sex ( <i>n</i> (%))        |                                   |                                    |                                    |          |
| Men                        | 396 (74.0)                        | 174 (76.30)                        | 222 (72.5)                         | 0.370    |
| Women                      | 139 (26.0)                        | 55 (24.0)                          | 84 (27.5)                          |          |
| BSA (m <sup>2</sup> )      | 1.82 ± 0.20                       | 1.83 ± 0.23                        | 1.76 ± 0.38                        | 0.012    |
| BMI (kg/m <sup>2</sup> )   | 27.2 ± 4.5                        | 26.6 ± 4.4                         | 27.6 ± 4.5                         | 0.050    |
| BMI ≥ 30 kg/m <sup>2</sup> | 124 (23.2)                        | 44 (19.2)                          | 80 (26.1)                          | 0.060    |
| LVEF, %                    | 34.3 ± 12.5                       | 23.5 ± 6.4                         | 42.1 ± 9.9                         | -        |
| Type 2 Diabetes Mellitus   | 189 (35.3)                        | 79 (34.5)                          | 110 (35.9)                         | 0.728    |
| Ischemic Heart Disease     | 302 (56.4)                        | 115 (50.2)                         | 187 (61.1)                         | 0.012    |
| Hypertension               | 372 (69.5)                        | 140 (61.1)                         | 232 (75.8)                         | <0.001   |
| Previous Cardiac Surgery   | 89 (16.6)                         | 30 (13.1)                          | 59 (19.3)                          | 0.058    |
| Hemodialysis               | 9 (1.7)                           | 3 (1.3)                            | 6 (2.0)                            | 0.739    |
| Creatinine (mg/dL)         | 1.37 ± 0.57                       | 1.34 ± 0.51                        | 1.40 ± 0.61                        | 0.268    |

Table 1. Cont.

| Variable                          | Total FMR Group<br><i>n</i> = 535 | FE < 30%<br><i>n</i> = 229 (42.8%) | FE ≥ 30%<br><i>n</i> = 306 (57.2%) | <i>p</i> |
|-----------------------------------|-----------------------------------|------------------------------------|------------------------------------|----------|
| eGFR (mL/min)                     | 62.2 ± 25.8                       | 62.8 ± 23.2                        | 61.7 ± 27.6                        | 0.763    |
| NYHA Class                        |                                   |                                    |                                    |          |
| I                                 | 12(2.2)                           | 4(1.7)                             | 8(2.6)                             | 0.348    |
| II                                | 59(11.0)                          | 22(9.6)                            | 37(12.1)                           |          |
| III                               | 355 (66.4)                        | 149 (65.1)                         | 206 (67.3)                         |          |
| IV                                | 109 (20.4)                        | 54 (23.6)                          | 55 (18.0)                          |          |
| STS Score                         | 3.7 (1.8–6.7)                     | 3.2 (1.6–6.4)                      | 3.6 (2.1–6.8)                      | 0.135    |
| Active Endocarditis               | 4 (0.7)                           | 1 (0.4)                            | 3 (1.0)                            | 0.639    |
| TAPSE                             | 14.9 ± 6.7                        | 15.6 ± 5.5                         | 14.4 ± 7.3                         | 0.109    |
| Dyslipidemia                      | 305 (57.0)                        | 131 (57.2)                         | 174 (56.9)                         | 0.937    |
| Critical Preoperative Status      | 28 (5.2)                          | 16 (7.0)                           | 12 (3.9)                           | 0.115    |
| Extracardiac Arteriopathy         | 73 (13.6)                         | 32 (14.0)                          | 41 (13.4)                          | 0.848    |
| Unstable Angina                   | 16 (3.0)                          | 7 (3.1)                            | 9 (2.9)                            | 0.938    |
| Permanent Atrial Fibrillation     | 313 (58.5)                        | 123 (53.7)                         | 190 (62.1)                         | 0.052    |
| Urgent Cardiac Surgery            | 49 (9.2)                          | 19 (8.3)                           | 30 (9.8)                           | 0.550    |
| Smoker                            | 154 (28.8)                        | 59 (25.8)                          | 95 (31.0)                          | 0.182    |
| COPD                              | 111 (20.7)                        | 45 (19.7)                          | 66 (21.6)                          | 0.588    |
| Recent Myocardial Infarction      | 41 (7.7)                          | 17 (7.4)                           | 24 (7.8)                           | 0.857    |
| Permanent Pacemaker               | 74 (13.8)                         | 32 (14.0)                          | 42 (13.7)                          | 0.934    |
| Stroke                            | 58 (10.8)                         | 26 (11.4)                          | 32 (10.5)                          | 0.741    |
| Percutaneous revascularization    | 210 (39.3)                        | 85 (37.1)                          | 125 (40.8)                         | 0.382    |
| CABG                              | 88 (16.4)                         | 23 (10.0)                          | 65 (21.2)                          | 0.001    |
| Cardiac Resynchronization         | 83 (15.5)                         | 51 (22.3)                          | 32 (10.5)                          | <0.001   |
| Autoimplantable<br>cardioverter   | 178 (33.3)                        | 109 (47.6)                         | 69 (22.5)                          | <0.001   |
| Prior TAVI                        | 13 (2.4)                          | 7 (3.1)                            | 6 (2.0)                            | 0.415    |
| Poor Morbidity                    | 52 (9.7)                          | 23 (10.0)                          | 29 (9.5)                           | 0.827    |
| Previous Heart<br>Transplantation | 29 (5.4)                          | 14 (6.1)                           | 15 (4.9)                           | 0.540    |
| Prior Mitral Annuloplasty         | 10 (1.9)                          | 3 (1.3)                            | 7 (2.3)                            | 0.528    |
| Aortic Surgery                    | 15 (2.8)                          | 3 (1.2)                            | 12 (3.9)                           | 0.070    |
| Technical Procedural Success      | 502 (93.8)                        | 214 (93.4)                         | 288 (94.1)                         | 0.751    |

BMI, body mass index; BSA, Body surface area; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TAVI, transcatheter aortic valve implantation. Recent MI is defined as happening between 7 and 30 days ago. Poor morbidity was an indirect measure of frailty based on the medical history (slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity or loss of independence).

Values represent *n* (%), mean ± standard deviation or median (interquartile range).

With the use of the propensity score, 144 patients who underwent TMVR with a LVEF <30% (group 1) were matched with 144 LVEF ≥30% (group 2) (global matched group 288, Table S1 supplementary material). The flow chart of the design of the study is shown in Figure 1.

After matching, the mean standardized differences were less than 10% for all variables, indicating marginal differences between the two groups (Table 2).

**Table 2.** Baseline characteristics of propensity score matched group and among both groups according to the LVEF.

|                            | Matched Group<br><i>n</i> = 288 | FE < 30%<br>(Group 1)<br><i>n</i> = 144 | FE ≥ 30%<br>(Group 2)<br><i>n</i> = 144 | <i>p</i> |
|----------------------------|---------------------------------|-----------------------------------------|-----------------------------------------|----------|
| Age (years)                | 71.5 ± 9.8                      | 71.3 ± 10.5                             | 71.8 ± 9.1                              | 0.676    |
| Sex ( <i>n</i> (%))        |                                 |                                         |                                         |          |
| Men                        | 228 (79.2)                      | 114 (79.2)                              | 114 (79.2)                              | -        |
| Women                      | 60 (20.8)                       | 30 (20.8)                               | 30 (20.8)                               |          |
| BSA (m <sup>2</sup> )      | 1.75 ± 0.36                     | 1.79 ± 0.19                             | 1.71 ± 0.48                             | 0.140    |
| BMI (kg/m <sup>2</sup> )   | 26.5 ± 4.2                      | 26.4 ± 4.0                              | 26.6 ± 4.3                              | 0.736    |
| BMI ≥ 30 kg/m <sup>2</sup> | 54 (18.8)                       | 27 (18.8)                               | 27 (18.8)                               | -        |



Table 2. Cont.

|                                       | Matched Group<br><i>n</i> = 288 | FE < 30%<br>(Group 1)<br><i>n</i> = 144 | FE ≥ 30%<br>(Group 2)<br><i>n</i> = 144 | <i>p</i> |
|---------------------------------------|---------------------------------|-----------------------------------------|-----------------------------------------|----------|
| LVEF, %                               | 32.9 ± 11.8                     | 24.2 ± 5.9                              | 41.6 ± 9.6                              | -        |
| Type 2 Diabetes Mellitus              | 96 (33.3)                       | 48 (33.3)                               | 48 (33.3)                               | -        |
| Ischemic Heart Disease                | 186 (64.6)                      | 93 (64.6)                               | 93 (64.6)                               | -        |
| Hypertension                          | 204 (70.8)                      | 102 (70.8)                              | 102 (70.8)                              | -        |
| Previous Cardiac Surgery              | 53 (18.4)                       | 25 (17.4)                               | 28 (19.4)                               | 0.648    |
| Hemodialysis                          | 7 (2.4)                         | 2 (1.4)                                 | 5 (3.5)                                 | 0.447    |
| Creatinine (mg/dL)                    | 1.39 ± 0.61                     | 1.38 ± 0.49                             | 1.41 ± 0.71                             | 0.643    |
| eGFR (mL/min)                         | 65.1 ± 29.0                     | 63.0 ± 24.8                             | 67.1 ± 32.6                             | 0.433    |
| NYHA Class                            |                                 |                                         |                                         |          |
| I                                     | 5 (1.7)                         | 1 (0.7)                                 | 4 (2.8)                                 | 0.115    |
| II                                    | 28 (9.7)                        | 11 (7.6)                                | 17 (11.8)                               |          |
| III                                   | 190 (66.0)                      | 93 (64.6)                               | 97 (67.4)                               |          |
| IV                                    | 65 (22.6)                       | 39 (27.1)                               | 26 (18.1)                               |          |
| STS Score                             | 3.9 (1.3–6.8)                   | 3.7 (1.9–7.2)                           | 3.5 (1.5–6.5)                           | 0.511    |
| Active Endocarditis                   | 1 (0.3)                         | 0                                       | 1 (0.7)                                 | 1        |
| TAPSE                                 | 14.7 ± 6.8                      | 15.1 ± 6.3                              | 14.8 ± 7.7                              | 0.274    |
| Dyslipidemia                          | 169 (58.7)                      | 88 (61.1)                               | 81 (56.3)                               | 0.402    |
| Critical Preoperative Status          | 13 (4.5)                        | 8 (5.6)                                 | 5 (3.5)                                 | 0.394    |
| Extracardiac Arteriopathy             | 46 (16.0)                       | 21 (14.6)                               | 25 (17.4)                               | 0.520    |
| Unstable Angina                       | 10 (3.5)                        | 5 (3.5)                                 | 5 (3.5)                                 | 1        |
| Permanent Atrial Fibrillation         | 163 (56.6)                      | 80 (55.6)                               | 83 (57.6)                               | 0.721    |
| Urgent Cardiac Surgery                | 22 (7.6)                        | 9 (6.3)                                 | 13 (9.0)                                | 0.375    |
| Smoker                                | 83 (28.8)                       | 43 (29.9)                               | 40 (27.8)                               | 0.696    |
| Chronic obstructive pulmonary disease | 56 (19.4)                       | 29 (20.1)                               | 27 (18.8)                               | 0.766    |
| Recent Myocardial Infarction          | 22 (7.6)                        | 10 (6.9)                                | 12 (8.3)                                | 0.825    |
| Permanent Pacemaker                   | 44 (15.3)                       | 22 (15.3)                               | 22 (15.3)                               | 1        |
| Stroke                                | 34 (11.8)                       | 18 (12.5)                               | 16 (11.1)                               | 0.715    |
| Percutaneous revascularization        | 129 (44.8)                      | 67 (46.5)                               | 62 (43.1)                               | 0.554    |
| CABG                                  | 54 (18.8)                       | 20 (13.9)                               | 34 (23.6)                               | 0.035    |
| Cardiac                               | 42 (14.6)                       | 26 (18.1)                               | 16 (11.1)                               | 0.095    |
| Resynchronization                     |                                 |                                         |                                         |          |
| Autoimplantable                       | 91 (31.6)                       | 61 (42.4)                               | 30 (20.8)                               | <0.001   |
| Cardiodefibrillator                   |                                 |                                         |                                         |          |
| Prior TAVI                            | 8 (2.8)                         | 6 (4.2)                                 | 2 (1.4)                                 | 0.282    |
| Poor Morbidity                        | 26 (9.0)                        | 13 (9.0)                                | 13 (9.0)                                | 1        |
| Previous Heart Transplantation        | 14 (4.9)                        | 7 (4.9)                                 | 7 (4.9)                                 | 1        |
| Prior Mitral annuloplasty             | 4 (1.4)                         | 2 (1.4)                                 | 2 (1.4)                                 | 1        |
| Surgery Aorta                         | 7 (2.4)                         | 2 (1.4)                                 | 5 (3.5)                                 | 0.447    |
| Technical Procedural Success          | 271 (94.1)                      | 135 (93.8)                              | 136 (94.4)                              | 0.803    |

BMI, body mass index; BSA, Body surface area; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TAVI, transcatheter aortic valve implantation. Recent MI is defined as happening between 7 and 30 days ago. Poor morbidity was an indirect measure of frailty based on the medical history (slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity or loss of independence).

Values represent *n* (%), mean ± standard deviation or median (interquartile range).

There were no significant differences among groups regarding the variables associated with the procedure (Table 3).

**Table 3.** Procedure-related variables.

|                                                          | Matched Group<br><i>n</i> = 288 | FE < 30%<br>(Group 1)<br><i>n</i> = 144 | FE ≥ 30%<br>(Group 2)<br><i>n</i> = 144 | <i>p</i> |
|----------------------------------------------------------|---------------------------------|-----------------------------------------|-----------------------------------------|----------|
| Procedural success, <i>n</i> (%)                         | 271 (94.1)                      | 135 (93.8)                              | 136 (94.4)                              | 0.803    |
| Number of clips implanted, <i>n</i>                      | 1.49 ± 0.64                     | 1.48 ± 0.64                             | 1.50 ± 0.64                             | 0.744    |
| Procedural duration, min                                 | 140 (115–180)                   | 141 (118–192)                           | 136 (105–179)                           | 0.413    |
| Implantation time, min                                   | 80 (60–107)                     | 82 (59–108)                             | 70 (60–108)                             | 0.677    |
| Degree of mitral regurgitation post clip, <i>n</i> (%)   |                                 |                                         |                                         |          |
| 0                                                        | 17 (5.9)                        | 9 (6.3)                                 | 8 (5.6)                                 | 0.955    |
| I                                                        | 176 (61.1)                      | 86 (59.7)                               | 90 (62.5)                               |          |
| II                                                       | 81 (28.1)                       | 41 (28.5)                               | 40 (27.8)                               |          |
| III                                                      | 8 (2.8)                         | 5 (3.5)                                 | 3 (2.1)                                 |          |
| IV                                                       | 6 (2.1)                         | 3 (2.1)                                 | 3 (2.1)                                 |          |
| Transmitral gradient after the clip, mmHg                | 3.05 ± 1.68                     | 3.06 ± 1.49                             | 3.04 ± 1.84                             | 0.923    |
| Clip detachment (partial or complete),                   | 8 (2.8)                         | 5 (3.5)                                 | 3 (2.1)                                 | 0.723    |
| Catheter thrombosis, <i>n</i> (%)                        | 2 (0.7)                         | 1 (0.7)                                 | 1 (0.7)                                 | 1        |
| Subvalvular chordal rupture <i>n</i> (%)                 | 3 (1.0)                         | 1 (0.7)                                 | 2 (1.4)                                 | 0.999    |
| Clip entanglement in subvalvular apparatus, <i>n</i> (%) | 0                               | 0                                       | 0                                       | -        |
| Puncture site hematoma, <i>n</i> (%)                     | 10 (3.5)                        | 5 (3.5)                                 | 5 (3.5)                                 | 1        |
| Arteriovenous fistula, <i>n</i> (%)                      | 3 (1.0)                         | 2 (1.4)                                 | 1 (0.7)                                 | 0.999    |
| Valvular surgery, <i>n</i> (%)                           | 1 (0.3)                         | 0                                       | 1 (0.7)                                 | 0.999    |
| Hemorrhage (BARC criteria)                               |                                 |                                         |                                         |          |
| 0                                                        | 250 (86.8)                      | 133 (92.4)                              | 117 (81.3)                              | 0.590    |
| 1                                                        | 32 (11.1)                       | 9 (6.3)                                 | 23 (16.0)                               |          |
| 2                                                        | 2 (0.7)                         | 1 (0.7)                                 | 1 (0.7)                                 |          |
| 3a                                                       | 1 (0.3)                         | 0                                       | 1 (0.7)                                 |          |
| 3b                                                       | 3 (1.0)                         | 1 (0.7)                                 | 2 (1.4)                                 |          |
| Pericardial leak                                         | 5 (1.7)                         | 3 (2.1)                                 | 2 (1.4)                                 | 0.685    |
| Urgent indication, <i>n</i> (%)                          | 19 (6.6)                        | 10 (6.9)                                | 9 (6.3)                                 | 0.812    |

Values represent *n* (%), mean ± standard deviation or median (interquartile range).

## 4. Outcomes

### 4.1. Primary Endpoint

The number of events for the primary study endpoint at 12 months of follow-up in group 1 was 48 (33.3) and 28 (19.4) in group 2, and the difference among both groups was statistically significant ( $p = 0.002$ ). The number of events for the combined endpoint at 12 months in the global matched group was 76 (26.4%).

The all-cause mortality was distributed according to LVEF as follows: 25 patients (17.4%) in group 1 and 10 patients in group 2 (6.9%). Significant differences were found among both groups for this outcome ( $p = 0.005$ ). The all-cause mortality in the global matched group was 12.2% (35 patients). There were 27 (9.4%) patients who died due to cardiac causes and four (1.4) of them suffered arrhythmic death. There were 8 (2.8%) non-cardiac deaths during the follow up (three Sepsis, three Cancer, one multiorgan failure and one suicide). The causes of death across the groups are detailed in Table 4.

The proportion of unplanned readmissions for HF was 18.4% in the global matched group. The proportion was 20.8% in the in group 1 (30 patients), whereas it was 16.0% (23 patients) in group 2 ( $p = 0.114$ ).

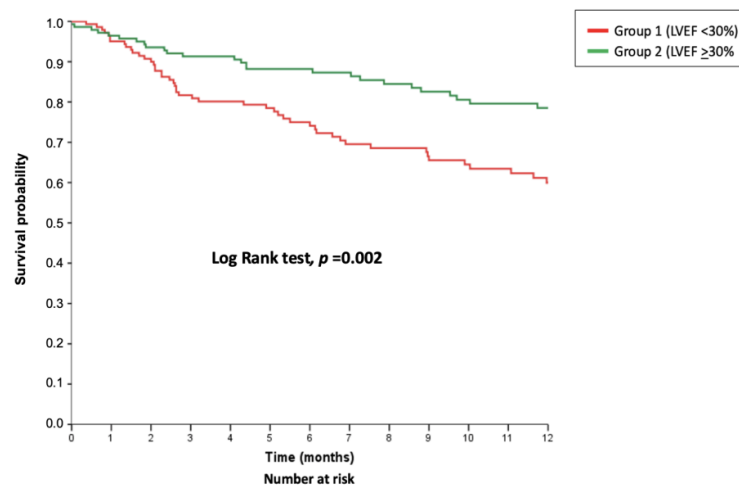
Median time to first readmission was 2.7 (1.5–6.0) in group 1 and 2.8 (1.2–7.3) in group 2 ( $p = 0.921$ ). Figure 2 shows the 12-month survival curves for the composite endpoint (Figure 2A), all-cause mortality (Figure 2B), and readmissions for HF (Figure 2C), according to LVEF.



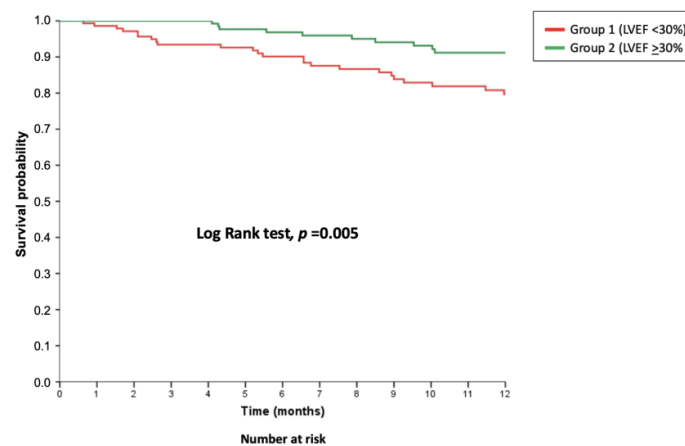
**Table 4.** Causes of death.

|                   | Matched<br>Group<br><i>n</i> = 288 | FE < 30%<br>(Group 1)<br><i>n</i> = 144 | FE ≥ 30%<br>(Group 2)<br><i>n</i> = 144 | <i>p</i> |
|-------------------|------------------------------------|-----------------------------------------|-----------------------------------------|----------|
| Deaths            | 35 (12.2)                          | 25 (17.4)                               | 10 (6.9)                                | 0.007    |
| Cardiac death     | 27 (9.4)                           | 20 (13.9)                               | 7 (4.9)                                 | 0.009    |
| Arrhythmic death  | 4 (1.4)                            | 3 (2.1)                                 | 1 (0.7)                                 | 0.622    |
| Non cardiac death | 8 (2.8)                            | 5 (3.5)                                 | 3 (2.1)                                 | 0.723    |

Median time to death was 5.5 (2.3–9.0) months in group 1 and 7.2 (4.3–9.7) months in group 2 ( $p = 0.333$ ).

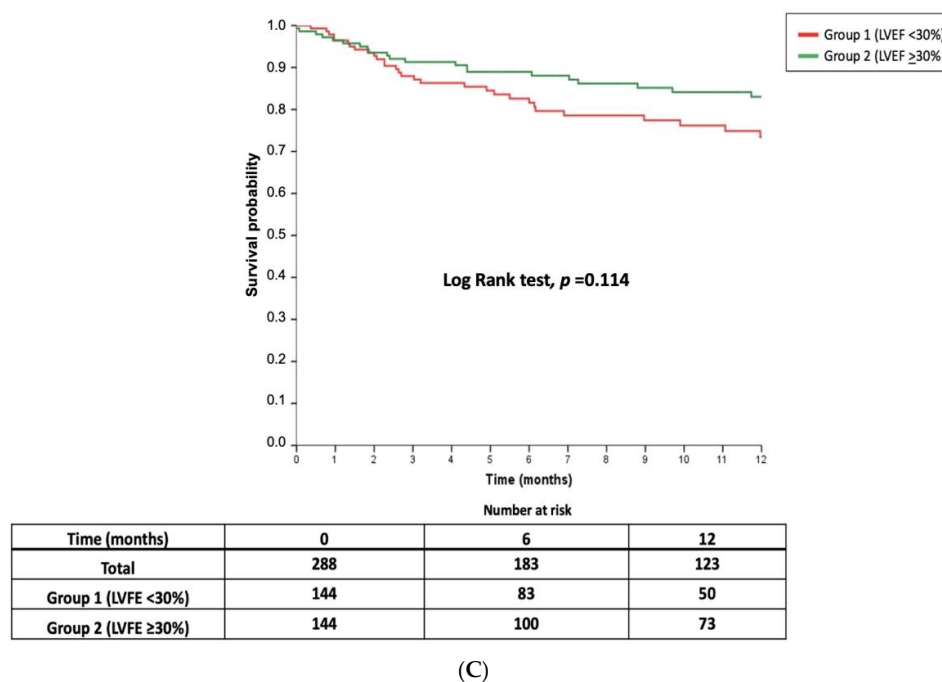


(A)



(B)

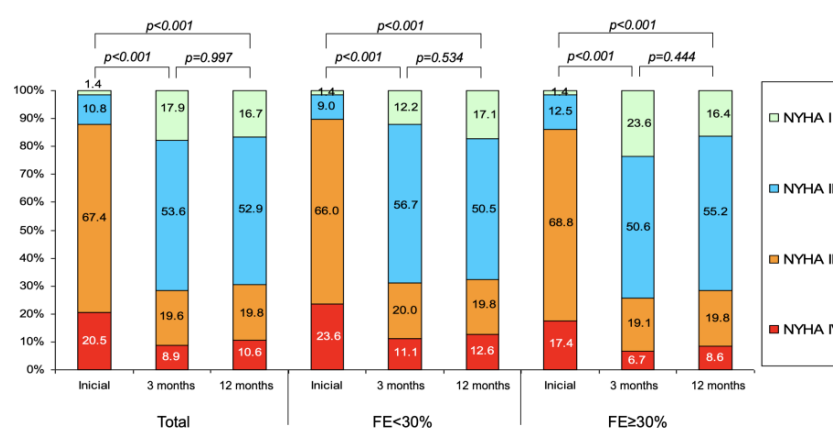
**Figure 2.** Cont.



**Figure 2.** Twelve-month survival curves for the composite event (A) Composite event (death/unplanned hospitalization), all-cause mortality. (B) All-cause mortality and readmission for heart failure (C) Readmission for heart failure according to LVEF groups.

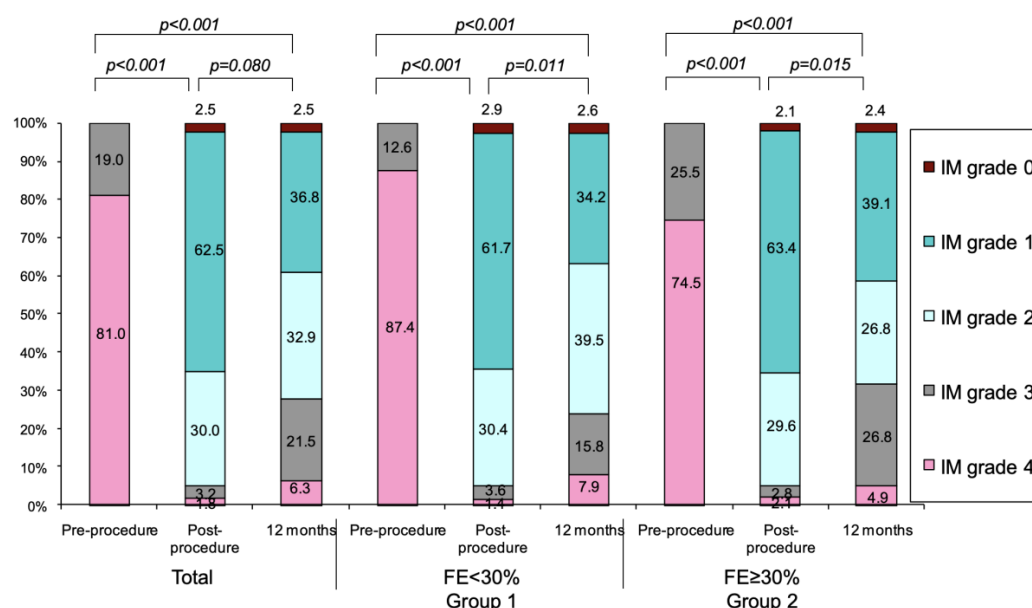
#### 4.2. Secondary Endpoints

Changes over time in the NYHA functional class are shown in Figure 3. There was a clear improvement at three months. This was maintained at 12 months of follow-up in both groups. At the end of follow-up, the proportion of patients in class  $\leq$  NYHA II was 67.6% in the group 1 and 71.6% in the group 2, without significant differences among them ( $p = 0.774$ ).



**Figure 3.** Modifications over time in NYHA functional class during follow-up in the entire series and according to LVEF. NYHA, New York Heart Association.

Regarding MR reduction (Figure 4), there was a clear improvement after the procedure, and it was maintained at one year. At the end of follow up, 76.3% of the patients in group 1 and 68.2% in group 2 had less or equal grade 2+ MR ( $p = 0.643$ ). During the follow up, four patients (one patient (0.7%) in group 1 and three patients (2.1%) in group 2,  $p = 0.622$ ) underwent conventional mitral valve surgery.



**Figure 4.** Changes over time in mitral regurgitation (MR) grade during follow-up in the entire series and according to LVEF groups. MR, mitral regurgitation.

## 5. Discussion

Our study highlights the relevance of severe LV dysfunction as a variable associated with death and rehospitalizations in a cohort of patients with FMR treated by percutaneous repair. LVEF should be a key element to analyze when selecting patients for this strategy. However, in spite of severe LV dysfunction, our paper shows that patients can still improve their functional clinical status. This is relevant also when dealing with this complex population, who are often short of therapeutic alternatives.

In the current study, we show that patients with FMR and severe LV dysfunction treated with MitraClip® have higher combined mortality and readmissions than patients without severe LV dysfunction treated with the same device. However, these patients showed no significant differences in the unplanned HF rehospitalization. Both groups showed significant improvement in the degree of MR and in the functional NYHA class. Our findings are in the line with previous registries regarding the prognosis implication of LVEF in patients treated with TMVR [10,11].

The association between the severity of left ventricular dysfunction and clinical outcomes following intervention with MitraClip® was established using a meta-regression in a recent metanalysis, partially explaining the contradicting results observed in the COAPT and the MITRA-FR trial [26].

Results from other interesting metanalyses highlighted the possible association between LV impairment and relative risk of all-cause and cardiovascular mortality, suggesting that patients with poor LVEF probably benefit less from TVMR [27].

The global clinical improvement after Mitraclip® in FMR remains under permanent study. While two recent observational studies showed worse outcomes in patients with lower LVEF [28,29], other reports have recently showed that the treatment with MitraClip® for FMR in patients with different degrees of LV dysfunction is associated with a considerable reduction of death and HF hospitalization at mid-term follow-up [30].

Both groups of our study had significant improvements after TVMR with Mitraclip® in the NYHA functional class and reduction in the grade of MR at the end of the follow-up. These results agree with previous reports of multinational real-life registries, where high rates of sustained MR reduction and clinical benefit were found also in patients with impaired LVEF [10–12,31]. Moreover, this could be a relevant point to take into account in order to consider the value of TMVR, not only for the improvement of prognosis in not-advanced stages of the disease, but also for the improvement in the quality of life of these patients in the follow up [32,33].

According to the results of our study, the prognostic implication of severe LV dysfunction in FMR patients should be considered in the selection of candidates for TMVR. In order to improve the prognosis of our patients, we should consider anticipating the treatment before severe deterioration in LVEF, as it was shown in the clinical trials [13,14]. However, we have to take into account that the severe impairment of LVEF should not contraindicate TMVR with Mitraclip®, because of the improvement in functional class and quality of life obtained in these symptomatic patients.

## 6. Limitations

Some limitations of our analysis should be considered. This was a non-randomized, observational study, and hence, it suffers from potential selection and ascertainment bias, despite robust propensity score matching. It is possible that some patients were lost on follow-up; however, this is an inherent limitation of all observational studies and we tried compensate this fact with a thorough clinical and echographic follow-up of all patients.

## 7. Conclusions

The careful selection of patients with FMR may be the most critical factor to predict favorable outcomes with the MitraClip® device. Therefore, it is very important to identify patients who could really benefit from TVMR in terms of prognosis. LVEF could be one of the most important variables. Patients with severe LV dysfunction treated with MitraClip® have higher mortality and readmissions than patients without severe dysfunction when treated with the same device. However, both groups obtain functional-class clinical benefit.

**Supplementary Materials:** The following are available online at <http://www.mdpi.com/2077-0383/9/6/1792/s1>, Table S1. Baseline characteristics of global FMR group and propensity score matched group.

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## 10.2. Anexo 2

MitraClip in secondary mitral regurgitation as a bridge to heart transplantation: 1-year outcomes from the international MitraBridge Registry.

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## ORIGINAL CLINICAL SCIENCE

# MitraClip in secondary mitral regurgitation as a bridge to heart transplantation: 1-year outcomes from the International MitraBridge Registry

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**KEYWORDS:**

MitraClip;  
secondary mitral  
regurgitation;  
advanced heart failure;  
heart transplantation;  
transcatheter mitral  
valve intervention

**BACKGROUND:** Patients awaiting heart transplantation (HTx) often need bridging therapies to reduce worsening and progression of underlying disease. Limited data are available regarding the use of the MitraClip procedure in secondary mitral regurgitation for this clinical condition.

**METHODS:** We evaluated an international, multicenter (17 centers) registry including 119 patients (median age: 58 years) with moderate-to-severe or severe secondary mitral regurgitation and advanced heart failure (HF) (median left ventricular ejection fraction: 26%) treated with MitraClip as a bridge strategy according to 1 of the following criteria: (1) patients active on HTx list (in list group) ( $n = 31$ ); (2) patients suitable for HTx but awaiting clinical decision (bridge to decision group) ( $n = 54$ ); or (3) patients not yet suitable for HTx because of potentially reversible relative contraindications (bridge to candidacy group) ( $n = 34$ ).

**RESULTS:** Procedural success was achieved in 87.5% of cases, and 30-day survival was 100%. At 1 year, Kaplan–Meier estimates of freedom from the composite primary end-point (death, urgent HTx or left ventricular assist device implantation, first rehospitalization for HF) was 64%. At the time of last available follow-up (median: 532 days), 15% of patients underwent elective transplant, 15.5% remained or could be included in the HTx waiting list, and 23.5% had no more indication to HTx because of clinical improvement.

**CONCLUSIONS:** MitraClip procedure as a bridge strategy to HTx in patients with advanced HF with significant mitral regurgitation was safe, and two thirds of patients remained free from adverse events at 1 year. These findings should be considered exploratory and hypothesis-generating to guide further study for percutaneous intervention in high-risk patients with advanced HF.

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Heart transplantation (HTx) is an effective therapeutic option for patients with advanced chronic heart failure (HF). However, increasing numbers of patients with refractory chronic HF and decreased availability of organs have resulted in expanded waiting lists and prolonged waiting times for patients listed for HTx.<sup>1</sup> More than 60% of patients are transplanted in high-urgency status<sup>2</sup> (Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] profile 1 and 2), leaving little chance for patients listed for less urgent transplantation (INTERMACS profile 3–7); notably, the mortality rate on the Eurotransplant waiting list in 2019 was 13% at 1 year and 19% up to 3 years.<sup>1</sup> Despite pharmacological measures, several bridging therapies, including mechanical circulatory support, have been implemented during the waiting period to improve the general condition of patients by helping reverse worsening end-organ function<sup>3</sup> and preventing sustained ventricular arrhythmias.<sup>4</sup> Currently, limited data are available regarding the use of MitraClip in patients with significant mitral regurgitation (MR) and advanced HF waiting for heart transplantation.<sup>5–10</sup> The aim of this multicenter registry is to report on the safety and efficacy of the percutaneous MitraClip procedure as a bridge strategy to HTx in a larger number of patients with advanced HF and concomitant moderate-to-severe or severe secondary MR.

## Methods

### Registry study design

MitraBridge is a multicenter observational registry, including all consecutive patients with chronic advanced HF (defined as New York Heart Association [NYHA] III or IV and/or left ventricular ejection fraction [LVEF]  $\leq 30\%$  and according to the recently updated definitions proposed by the Heart Failure Association of

the European Society of Cardiology<sup>3</sup>) and concomitant moderate-to-severe or severe secondary (or functional) MR being potential candidates for HTx. The registry was initiated in June 2018 without the support of any external funding and has been designed to collect data from centers with experience in transcatheter MitraClip treatment (Abbott Vascular, Santa Clara, CA). A total of 17 centers from Europe and Canada contributed to the registry. Baseline and follow-up data (the latter according to study centers' availability) were collected through the use of a prospectively maintained database. The inclusion of patients in this study was approved at each institution by a local ethical committee or per local practice for the collection of prospective data. This study is registered with ClinicalTrials.gov (NCT04293575).

### Patient selection and definitions

All potential candidates for HTx treated with MitraClip in the context of a pre-specified bridge strategy were classified according to 1 of the following clinical conditions present at the time of MitraClip procedure:

1. patients active on an HTx list (in list group) with a low likelihood to receive an organ rapidly (e.g., for blood group) and/or progressive unstable clinical conditions;
2. patients with new unexpected clinical worsening and/or new history of acute HF decompensation, who were otherwise suitable for HTx (according to local heart team evaluation) but were still waiting for final clinical decision (bridge to decision [BTD] group); or
3. patients who could not be yet be listed for HTx (bridge to candidacy [BTC] group) because of concomitant, potentially reversible contraindications, such as severe pulmonary hypertension, elevated pulmonary vascular resistance, unsatisfactory response to vasodilator challenge or other causes resulting in a prohibitive periprocedural risk (e.g., pre-transplant body mass index

>35 kg/m<sup>2</sup>, severe renal dysfunction with creatinine clearance <30 ml/min), and other reasons (current alcohol, tobacco, or drug abuse; poor social support; non-residents) (Figure 1). All patients were considered as high-risk surgical candidates because of advanced HF. Only patients with mitral valve anatomy suitable for percutaneous mitral valve repair using the MitraClip device were included. No exclusion criteria were applied according to baseline patient INTERMACS profiles. Grading of the severity of MR was assessed using a combination of semi-quantitative and quantitative assessment, as described by the American Society of Echocardiography guidelines and the European Association of Echocardiography guidelines.<sup>11,12</sup>

## Study end-points

The primary end-point was the 1-year composite adverse events rate of all-cause death, urgent HTx or left ventricular assist device (LVAD) implantation, and first rehospitalization for HF. As secondary end-point, we included the rate of first rehospitalization for HF within the first year after MitraClip procedure. Moreover, we described the clinical status of patients at the time of last available follow-up to report the rates of patients entering (or remaining) in the waiting list, having no more indication to HTx because of significant echocardiographic and/or clinical improvements during the entire observational period, and going for elective HTx. Mitral Valve Academic Research Consortium criteria were used to define procedural success and composite events.<sup>13</sup> After the procedure, patients were prospectively evaluated at 1 month and 1 year and then according to the time frame elapsed from the index procedure to data lock for present analysis. For patients who underwent LVAD implantation, the follow-up time was stopped at the date of mechanical device placement.

## Statistical analysis

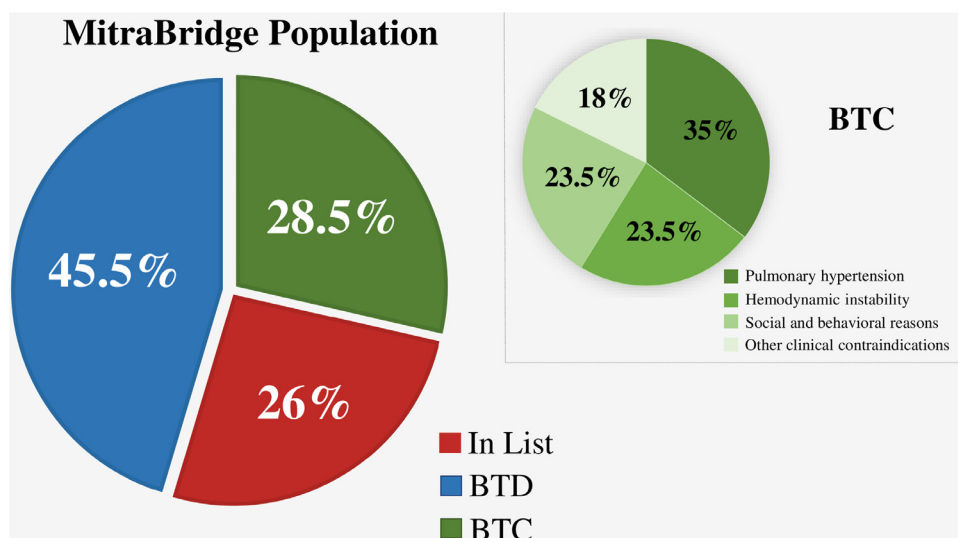
Results are presented as mean  $\pm$  SD for continuous variables normally distributed (tested by the Shapiro-Wilk normality test), as

median (25th and 75th percentiles) for continuous variables without normal distribution, and as percentages for categorical data. One-way analysis of variance and Student's unpaired *t*-test were used to compare normally distributed continuous variables. For non-normally distributed continuous variables, the Kruskal-Wallis test and Wilcoxon rank-sum test were used to compare data between 3 or 2 groups, respectively. Chi-square and Fisher exact tests were used to compare categorical variables. Survival was reported using the Kaplan–Meier method, and comparisons were performed using the log-rank test. A two-tailed *p*-value < 0.05 was considered statistically significant. Univariate analysis of predictors of the primary end-point was performed with Cox proportional hazards regression. All variables with a *p*-value < 0.10 and those considered clinically relevant (age and estimated glomerular filtration rate) were inserted in a multivariate Cox regression model to assess the hazard ratio (HR) and 95% confidence interval (CI) of the relationship between predictors and primary end-point. The convention of limiting the number of independent variables to 1 for every 10 events was followed.<sup>14</sup> The statistical analysis, the Kaplan–Meier mortality curves, and the graphs were performed with the use of Stata version 14 (StataCorp LLC, College Station, TX) and GraphPad Prism software version 6 (GraphPad, Inc, San Diego, CA).

## Results

### Study population and demographics

In the MitraBridge registry, 119 patients with moderate-to-severe or severe secondary MR and advanced HF across 17 centers (in Italy, Switzerland, the Netherlands, Spain, and Canada) have been included. The median age of the treated population was 58 years (25th–75th percentile: 51–63 years), with 59% of patients  $\leq$ 60 years old. Before MitraClip procedure, all patients were on guideline-directed medical therapy as tolerated (Table 1). Hospitalization for HF within the previous 6 months was reported in 61.5% of cases, with 36% of patients treated during rehospitalization with inotropic agents for circulatory support. Median N-terminal pro-B-type natriuretic peptide level at baseline was



**Figure 1** Clinical status according to heart transplantation list at the time of MitraClip procedure. BTC, bridge to candidacy; BTD, bridge to decision.

3,612.5 pg/ml (25th–75th percentile: 2,182.5–7,043.5 pg/ml). At the time of MitraClip procedure, 31 patients (26%) were on the active HTx list (in list group), 21 of them with progressive deterioration of clinical status, needing 1 or more rehospitalizations for HF in the 6 months before the procedure, and 10 patients with a stable clinical condition but a low likelihood to receive an organ shortly because of

heart size (4 patients) and blood group type (6 patients). A total of 54 patients (45.5%) were still waiting for final clinical decision (BTD group). Finally, 34 patients (28.5%) could not be yet be listed (BTC group) because of concomitant severe pulmonary hypertension and/or elevated pulmonary vascular resistance ( $n = 12$ ), severe hemodynamic instability ( $n = 8$ ; 2 patients with recurrent sustained

**Table 1** Baseline Clinical Characteristics

| Clinical characteristics                    | Overall( $n = 119$ ) | In list( $n = 31$ ) | BTD( $n = 54$ )  | BTC( $n = 34$ )  | <i>p</i> -value |
|---------------------------------------------|----------------------|---------------------|------------------|------------------|-----------------|
| Age, years                                  | 58 (51–63)           | 53 (43–61)          | 60 (55–64)       | 58.5 (43–63)     | 0.0016          |
| Age $\leq 60$ years                         | 70 (59)              | 23 (74)             | 28 (52)          | 19 (56)          | 0.121           |
| Male sex                                    | 91 (76.5)            | 25 (81)             | 41 (76)          | 25 (73.5)        | 0.790           |
| BMI, kg/m <sup>2</sup>                      | 25 (23.4–28.4)       | 25.3 (23.4–28.4)    | 24.7 (23.4–28.4) | 25.4 (22.5–28.7) | 0.963           |
| Hypertension                                | 51 (43)              | 10 (32)             | 27 (50)          | 14 (41)          | 0.274           |
| Diabetes                                    | 32 (27)              | 4 (13)              | 15 (28)          | 13 (38)          | 0.070           |
| Hypercholesterolemia                        | 62 (52)              | 17 (55)             | 28 (52)          | 17 (50)          | 0.926           |
| eGFR, ml/min                                | 67.1 (54–90)         | 71.7 (61.3–94.5)    | 59.5 (48.2–77.4) | 76.4 (57–100)    | 0.052           |
| eGFR $\leq 60$ ml/min                       | 43 (36)              | 6 (19)              | 27 (50)          | 10 (29.5)        | 0.011           |
| Atrial fibrillation                         | 42 (35)              | 17 (55)             | 14 (26)          | 11 (32.5)        | 0.025           |
| COPD                                        | 10 (8.5)             | 1 (3)               | 5 (9)            | 4 (12)           | 0.388           |
| NYHA class III–IV                           | 113 (95)             | 27 (87)             | 53 (98)          | 33 (97)          | 0.065           |
| Ischemic MR                                 | 57 (48)              | 12 (39)             | 28 (52)          | 17 (50)          | 0.485           |
| INTERMACS profiles                          |                      |                     |                  |                  | 0.288           |
| 1–2                                         | 4 (3.5)              | 0 (0)               | 3 (5.5)          | 1 (3)            |                 |
| 3–4                                         | 44 (37)              | 12 (39)             | 18 (33.5)        | 14 (41)          |                 |
| 5–6                                         | 52 (43.5)            | 16 (51.5)           | 20 (37)          | 16 (47)          |                 |
| 7                                           | 19 (16)              | 3 (9.5)             | 13 (24)          | 3 (9)            |                 |
| EuroSCORE II, %                             | 3.5 (2.6–6.2)        | 3.2 (2.2–7.1)       | 3.8 (3–7.5)      | 3.3 (2.3–4.8)    | 0.173           |
| Past medical history                        |                      |                     |                  |                  |                 |
| Previous AMI                                | 55 (46)              | 11 (35.5)           | 27 (50)          | 17 (50)          | 0.378           |
| Previous PCI                                | 46 (38.5)            | 11 (35.5)           | 21 (39)          | 14 (41)          | 0.894           |
| Previous CABG                               | 12 (10)              | 2 (6.5)             | 6 (11)           | 4 (12)           | 0.734           |
| Previous stroke                             | 9 (7.5)              | 2 (6.5)             | 6 (11)           | 1 (3)            | 0.356           |
| HF hospitalization within previous 6 months | 73 (61.5)            | 21 (68)             | 32 (59)          | 20 (59)          | 0.696           |
| GDMT at baseline                            |                      |                     |                  |                  |                 |
| ACE-I/ARB                                   | 85 (71.5)            | 25 (81)             | 33 (61)          | 27 (79.5)        | 0.075           |
| ARNI                                        | 18 (15)              | 6 (19)              | 11 (20.5)        | 1 (3)            | 0.063           |
| Beta-blocker                                | 106 (89)             | 31 (100)            | 45 (83.5)        | 30 (88)          | 0.060           |
| Ivabradine                                  | 20 (17)              | 4 (13)              | 11 (20.5)        | 5 (14.5)         | 0.626           |
| K sparing diuretics                         | 102 (85.5)           | 27 (87)             | 45 (83.5)        | 30 (88)          | 0.779           |
| Loop diuretics                              | 113 (95)             | 29 (93.5)           | 51 (94.5)        | 33 (97)          | 0.771           |
| ICD                                         | 91 (76.5)            | 28 (90.5)           | 33 (61)          | 30 (88)          | 0.002           |
| CRT                                         | 45 (38)              | 13 (42)             | 23 (42.5)        | 9 (26.5)         | 0.271           |
| Procedural outcomes                         |                      |                     |                  |                  |                 |
| Procedural success                          | 104 (87.5)           | 28 (90.5)           | 50 (92.5)        | 26 (76.5)        | 0.072           |
| N° clips                                    |                      |                     |                  |                  | 0.164           |
| 0                                           | 2 (1.5)              | 2 (6.5)             | 0 (0)            | 0 (0)            |                 |
| 1                                           | 38 (32)              | 8 (26)              | 20 (37)          | 10 (29.5)        |                 |
| 2                                           | 64 (54)              | 15 (48.5)           | 30 (55.5)        | 19 (56)          |                 |
| >3                                          | 15 (12.5)            | 6 (19)              | 4 (7.5)          | 5 (14.5)         |                 |

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; BTC, bridge to candidacy; BTD, bridge to decision; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Data are presented as absolute numbers and percentages (for categorical variables) and median value and 25th and 75th percentiles (for continuous variables).

ventricular tachycardia, 5 patients with persistent unstable hemodynamic condition requiring mechanical circulatory support and/or infusion of vasoactive drugs, and 1 patient with repeatedly unsuccessful weaning from mechanical ventilation), other clinical causes making the peri-procedural risk prohibitive ( $n=6$ ; 1 patient with pre-transplant body mass index  $>30$  kg/m<sup>2</sup>, 1 patient with severe renal dysfunction, 2 patients with diabetes complicated by severe vasculopathy, and 2 patients with new-onset neoplasia awaiting prognostic definition and treatment), or social and behavioral reasons ( $n=8$ ; 5 patients for current alcohol or tobacco abuse, 2 patients because they were non-residents, and 1 for poor social support) (Figure 1). According to INTERMACS classification, most patients were in profile 3 to 4 (37%) and 5 to 6 (43.5%), whereas 4 (3.5%) patients were in profile 1 to 2, requiring mechanical and pharmacological circulatory supports (Table 1).

### Echocardiography and right heart catheterization at baseline

All included patients had secondary MR owing to left ventricular dysfunction and remodeling. Median LVEF was 26% (25th–75th percentile: 20%–32%), and 71.5% of patients ( $n=85$ ) had an LVEF  $\leq 30\%$ . Median left ventricular end diastolic volume index (LVEDVi) and median left atrial volume index were 122.5 ml/m<sup>2</sup> (25th–75th percentile: 104.5–150.5 ml/m<sup>2</sup>) and 59 ml/m<sup>2</sup> (25th–75th percentile: 38–78.5 ml/m<sup>2</sup>), respectively, showing advanced left heart chambers remodeling. According to each study center's echocardiographic practice, a quantitative assessment of MR severity using the proximal isovelocity surface area radius method was available in 24.5% of patients ( $n=29$ ), with no statistical difference between the 3 groups: median effective regurgitant orifice area (EROA) and median regurgitant volume (RVol) were 30 mm<sup>2</sup> (25th–75th percentile: 25–40.5 mm<sup>2</sup>,  $p$ -value = 0.563) and 41 ml/beat (25th–75th percentile: 30–55 ml/beat,  $p$ -value = 0.932), respectively. Right ventricle dysfunction (defined as tricuspid annular plane systolic excursion  $<17$  mm) was observed in 28.5% of patients (overall tricuspid annular plane systolic excursion:  $17 \pm 4$  mm). Median systolic pulmonary artery pressure (sPAP) was 48.5 mm Hg (25th–75th percentile: 40–60 mm Hg) and 46% of patients had sPAP  $\geq 50$  mm Hg (Table 2). Pre-procedural right heart catheterization data were available for more than half of patients (65.5%), and they had homogeneous distribution within the study population (Table 2). Post-capillary pulmonary hypertension was the main pattern.

### MitraClip peri-procedural results

No deaths occurred during the MitraClip procedure. Procedural success was achieved in 87.5% of cases, with a higher success in those on the HTx list (90.5%) and BTd groups (92.5%) than in BTC group (76.5%;  $p=0.072$ ). Two patients could not be implanted because of inadequate clip positioning and the unfavorable device trajectory in a giant

left atrium, respectively (Table 1). The rate of 30-day mortality was 0%.

### Clinical outcome

The clinical follow-up was available for 116 patients (97.5%), within an overall median follow-up time of 532 days (25th–75th percentile: 188–986 days). After the MitraClip procedure, 13 patients (11%) died (median time: 610 days; 25th–75th percentile: 230–1,089 days): cardiac death occurred in 9 (69%) patients, mainly HF (67%) and sudden death (33%); 4 patients died because of non-cardiovascular causes (31%); 1 patient died of septic shock; 1 patient died of cancer; and 2 died because of unknown causes. Urgent HTx was necessary in 7 patients (6%). LVAD implantation was performed in 21 patients (18%) (median time: 483 days, 25th–75th percentile: 66–743 days) because of MitraClip bridge therapy failure with progressive clinical worsening: 19 patients received LVAD as bridge therapy, whereas 2 patients, who belonged to the BTC group because of new-onset neoplasia and poor social support, finally received LVAD as destination therapy.

Elective HTx was successfully performed in 17 patients (15%) at a median time of 477 days (25th–75th percentile: 181–602 days) after the MitraClip procedure; all patients were stable on oral medications and able to wait at home. Of these, 8 patients were on the HTx list before MitraClip implantation, 5 patients belonged to the BTd group, and 4 patients were in the BTC group (Figure 2). Clinical information after the transplant was available in 9 of 17 cases, with a median follow-up time of 628 days (25th–75th percentile: 279–899 days). Three patients died because of acute heart transplantation adverse events (2 HTx rejections and 1 from infectious complications) and 1 patient died secondary to septic shock 305 days after the transplant; in the other 5 cases, patients were still alive with optimal hemodynamic and functional status (NYHA class I or II).

A total of 27 patients (23.5%) no longer had an indication for HTx because of significant clinical improvement: 5 of these patients belonged to the in list group (delisted for clinical improvement), the other 22 to the BTd ( $n=12$ ) and BTC ( $n=10$ ) groups. All of them had residual MR grade  $\leq 2$  and experienced significant reduction of NYHA functional class at follow-up; particularly, no patient was in NYHA functional class IV, and an improvement of at least 1 NYHA class was observed in 24 patients (89%). Hospitalization for HF in the 6 months before the MitraClip procedure occurred in 14 patients (52%), whereas in the 6 months after the procedure, only 1 (4%) patient has been rehospitalized ( $p < 0.001$ ). The median LVEDVi and sPAP changed from 116 ml/m<sup>2</sup> (25th–75th percentile: 84–126 ml/m<sup>2</sup>) to 107.5 ml/m<sup>2</sup> (25th–75th percentile: 80–126.5 ml/m<sup>2</sup>;  $p=0.605$ ) and from 45 mm Hg (25th–75th percentile: 36–55 mm Hg) to 32 mm Hg (25th–75th percentile: 29–45 mm Hg;  $p=0.02$ ), respectively; values of LVEF remained stable, from 29% (25th–75th percentile: 25%–34%) to 29% (25th–75th percentile: 23%–36%;  $p=0.776$ ).



**Table 2** Echocardiographic and Right Heart Catheterization Characteristics

| Echocardiographic characteristics               | Overall( <i>n</i> = 119) | In list( <i>n</i> = 31) | BTD( <i>n</i> = 54) | BTC( <i>n</i> = 34) | <i>p</i> -value |
|-------------------------------------------------|--------------------------|-------------------------|---------------------|---------------------|-----------------|
| Mitral regurgitation                            |                          |                         |                     |                     | 0.985           |
| Moderate to severe (3+)                         | 15 (12.5)                | 4 (13)                  | 7 (13)              | 4 (12)              |                 |
| Severe (4+)                                     | 104 (87.5)               | 27 (87)                 | 47 (87)             | 30 (88)             |                 |
| LVEF, %                                         | 26 (20–32)               | 24 (20–31)              | 24 (20–30)          | 28.5 (25–34)        | 0.076           |
| LVEF ≤30%                                       | 85 (71.5)                | 23 (74)                 | 41 (76)             | 21 (62)             | 0.332           |
| LVEDVi, mL/m <sup>2</sup>                       | 122.5 (104.5–150.5)      | 121.5 (106–156)         | 126.5 (102–151)     | 118 (100–143)       | 0.634           |
| LVESVi, mL/m <sup>2</sup>                       | 86 (71.5–112)            | 87.5 (82.5–109)         | 94 (72.5–121)       | 83 (60.5–103)       | 0.275           |
| LVEDD, mm                                       | 71 ± 10                  | 71.5 ± 8.5              | 71 ± 10             | 70.5 ± 11           | 0.912           |
| LVESD, mm                                       | 61.5 ± 10.5              | 65 ± 10                 | 62 ± 10             | 59 ± 11             | 0.146           |
| LAVi, mL/m <sup>2a</sup>                        | 59 (38–78.5)             | 61.5 (23–77.5)          | 57 (38–79)          | 64 (51–79.5)        | 0.707           |
| sPAP, mm Hg                                     | 48.5 (40–60)             | 55 (45–70)              | 45 (38–55)          | 48.5 (40–60)        | 0.029           |
| sPAP ≥ 50 mm Hg                                 | 55 (46)                  | 21 (68)                 | 19 (35)             | 15 (44)             | 0.021           |
| Tricuspid regurgitation > 2 <sup>a</sup>        | 22 (18.5)                | 5 (16)                  | 8 (15)              | 9 (26.5)            | 0.595           |
| TAPSE, mm <sup>a</sup>                          | 17 ± 4                   | 17 ± 4                  | 17.5 ± 4.5          | 17.5 ± 3.5          | 0.761           |
| Basal RVD, mm <sup>a</sup>                      | 37.5 ± 10                | 42 ± 9                  | 40 ± 8              | 29 ± 9.5            | <0.001          |
| RH catheterization characteristics <sup>b</sup> | Overall( <i>n</i> = 78)  | In list( <i>n</i> = 23) | BTD( <i>n</i> = 33) | BTC( <i>n</i> = 22) | <i>p</i> -value |
| Cardiac index, liter/min/m <sup>2</sup>         | 1.9 (1.6–2.3)            | 1.9 (1.4–2.2)           | 2 (1.7–2.4)         | 1.9 (1.7–2.4)       | 0.505           |
| Cardiac index <2 liter/min/m <sup>2</sup>       | 47 (60)                  | 16 (70)                 | 18 (54.5)           | 13 (59)             | 0.524           |
| Wedge pressure, mm Hg                           | 26 ± 10                  | 27 ± 7.5                | 27 ± 11.5           | 23 ± 9              | 0.248           |
| Systolic PAP, mm Hg                             | 52 ± 16                  | 53 ± 12.7               | 48 ± 13.7           | 55.5 ± 21           | 0.373           |
| Diastolic PAP, mm Hg                            | 25 ± 7.8                 | 27.5 ± 5                | 24 ± 7              | 24.2 ± 10           | 0.350           |
| Mean PAP, mm Hg                                 | 34.5 ± 10                | 36 ± 7                  | 32.5 ± 9            | 35 ± 13             | 0.631           |
| Mean PAP ≥40 mm Hg                              | 16 (20.5)                | 6 (26)                  | 4 (12)              | 6 (27)              | 0.569           |
| PVR, WU                                         | 3.06 ± 2.7               | 2.6 ± 1.2               | 2.1 ± 2.4           | 3.9 ± 3.5           | 0.234           |
| PVRi, WU m <sup>2</sup>                         | 5.73 ± 5.5               | 4.8 ± 2.2               | 4 ± 4.6             | 7.4 ± 7.3           | 0.265           |
| TPG >12 mm Hg                                   | 8 (10)                   | 2 (8.5)                 | 2 (6)               | 4 (18)              | 0.605           |

Abbreviations: BTC, bridge to candidacy; BTD, bridge to decision; LAVi, left atrial volume index; LVEDD, left ventricular end diastolic diameter; LVEDVi, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESVi, left ventricular end systolic volume index; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; RH, right heart; RVD, right ventricular diameter; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; WU, Wood unit.

Data are presented as absolute numbers and percentages (for categorical variables) and mean value ± SD or median value and 25th and 75th percentiles (for continuous variables).

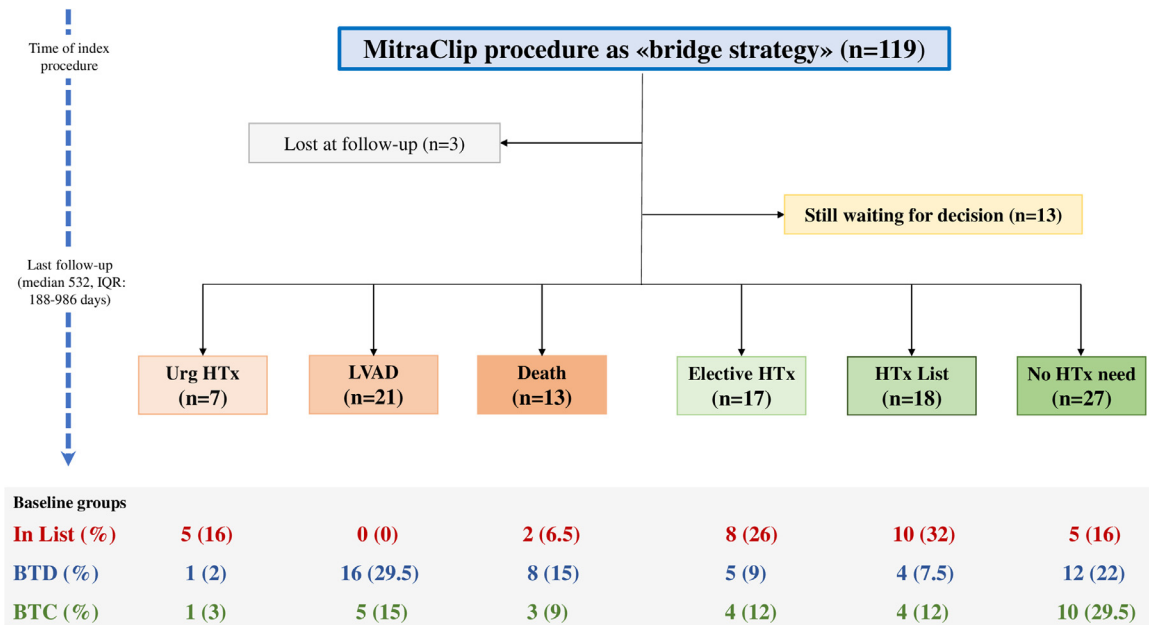
<sup>a</sup>Data for these parameters were not available for all patients.

<sup>b</sup>RH catheterization data were available for 78 (65.5%) patients.

Finally, whereas 10 patients (8.5%) remained in list for HTx, 8 patients (7%), previously belonging to the BTD (*n* = 4) and BTC (*n* = 4) groups, moved to the active HTx list. For BTC group patients, 3 of them, who had been previously excluded from the HTx list because of severe pulmonary hypertension with elevated right atrial pressure, became eligible for HTx owing to reduction of arterial pulmonary pressure; for the other patient, who had been temporarily excluded from the HTx list because of new-onset breast cancer, the MitraClip procedure allowed her to maintain a stable clinical condition until the eligibility for HTx was reconfirmed after neoplasia treatment. For all 4 patients in the BTD group, an end-stage HF condition needing HTx was confirmed, and MitraClip treatment guaranteed them to be eligible for elective transplant without new HF rehospitalization. Clinical conditions at the time of last available follow-up, stratified according to pre-defined baseline criteria, are presented in Figure 2. Regarding

the 2 patients unable to successfully have the procedure (both belonging to the in list group), both were rehospitalized for acute HF after the index procedure; one of them underwent urgent HTx after 152 days, whereas the other one is awaiting HTx.

The 1-year Kaplan–Meier estimates of freedom from composite of all-cause of death, urgent HTx or LVAD implantation, and first rehospitalization for HF (primary end-point) was 64% (Figure 3a). Within the first year of follow-up, 35 rehospitalizations for HF (30%), 5 all-cause deaths (4.5%), 7 urgent HTxs (6%), and 6 LVAD implantations (5%) occurred. The 1-year Kaplan–Meier estimates of freedom from secondary end-point (rehospitalization for HF) was 67% (Figure 3b) with no statistically significant difference among the 3 population groups (Figure 3c). Particularly, a far lower rate of rehospitalization in the 6 months after the intervention compared with the previous 6 months (24.5% vs 61.5%) was observed.

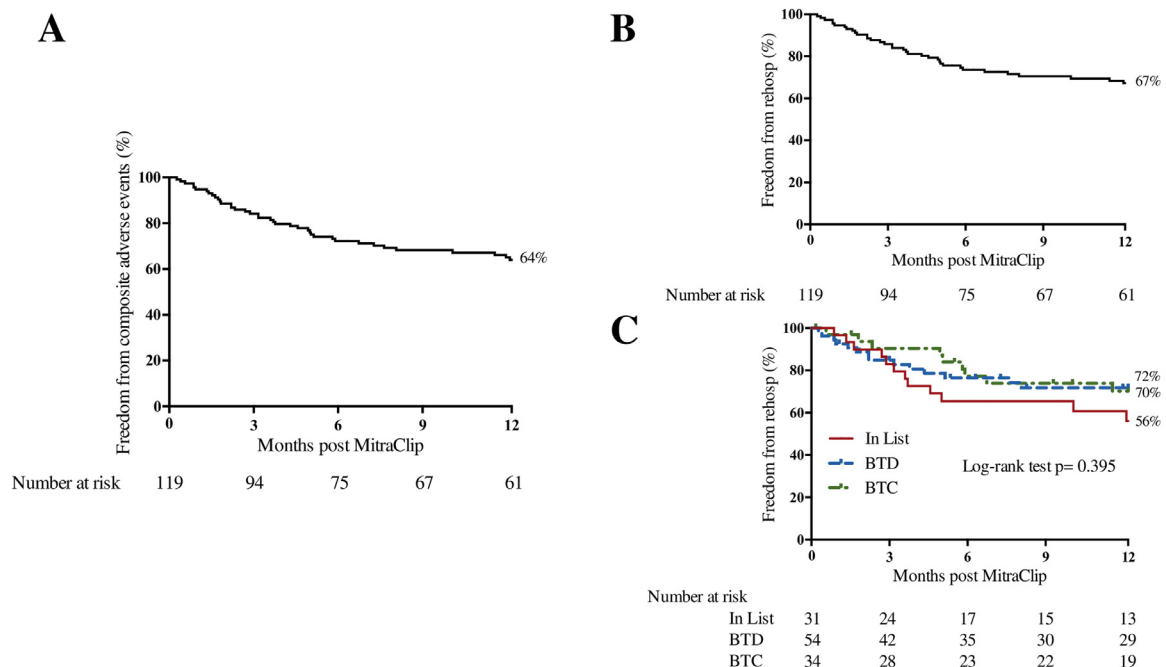


**Figure 2** Follow-up status stratified according to pre-defined baseline criteria. Stratified data according to pre-defined baseline criteria are presented as absolute numbers and percentages. BTC, bridge to candidacy; BTD, bridge to decision; HTx, heart transplantation; IQR, interquartile range; LVAD, left ventricular assist device; Urg, urgent.

At multivariable Cox regression analysis, post-procedural MR grade >2 (HR: 3.2; 95% CI: 1.4–7.3;  $p$ -value = 0.006), hospitalization for HF within 6 months before the procedure (HR: 2.9; 95% CI: 1.3–6.6,  $p$ -value = 0.009), and baseline INTERMACS profile 1 to 4 (HR: 2.7; 95% CI: 1.3–5.6;  $p$ -value = 0.008) were confirmed as independent predictors of the primary composite end-point (Table 3).

## Discussion

This is a multicenter, international registry reporting data in patients with advanced HF with significant secondary MR and the MitraClip procedure as a bridge to transplant strategy. The main findings demonstrate the following: (1) the selected use of MitraClip as a bridge strategy to HTx was safe (87.5% procedural success and no death at 30 days)



**Figure 3** Kaplan–Meier curves. (a) Primary composite end-point (all-cause death, urgent HTx or LVAD implantation, first rehossp for HF) at 1 year in the overall population. (b) Secondary end-point (first rehossp for HF) at 1 year in the overall population and (c) stratified by baseline clinical status. BTC, bridge to candidacy; BTD, bridge to decision; HF, heart failure; LVAD, left ventricular assist device; rehossp, rehospitalization.

**Table 3** Predictors of Univariate and Multivariate Cox Regression Analysis

| Predictor                       | Univariate      |         | Multivariate     |         |
|---------------------------------|-----------------|---------|------------------|---------|
|                                 | HR (95% CI)     | p-value | HR (95% CI)      | p-value |
| Age                             | 1 (0.97–1.03)   | 0.777   | 1.03 (0.99–1.07) | 0.124   |
| eGFR                            | 0.9 (0.98–1)    | 0.296   | 1 (0.98–1.01)    | 0.753   |
| Previous rehos. within 6 months | 3.2 (1.4–6.9)   | 0.003   | 2.9 (1.3–6.6)    | 0.009   |
| Procedural failure              | 2.5 (1.2–5.3)   | 0.015   | —                | —       |
| Residual MR >2                  | 3.1 (1.5–6.4)   | 0.002   | 3.2 (1.4–7.3)    | 0.006   |
| INTERMACS 1–4                   | 3.4 (1.8–6.6)   | <0.001  | 2.7 (1.3–5.6)    | 0.008   |
| LVEF                            | 0.95 (0.9–0.99) | 0.033   | —                | —       |
| LVESVi                          | 1.01 (1–1.02)   | 0.030   | —                | —       |
| Inotropic agents                | 1.9 (1–3.8)     | 0.037   | —                | —       |
| NYHA Class 4                    | 2.5 (1.3–4.6)   | 0.005   | —                | —       |

Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end systolic volume index; MR, mitral regurgitation; NYHA, New York Heart Association; rehos, rehospitalization.

and effective; (2) two thirds of patients remain free of development of composite adverse events at 1 year (primary end-point); (3) 15.5% became eligible for transplant; and (4) nearly a quarter could be removed from consideration for HTx because of clinical improvement.

These exploratory results are promising and support the further study of MitraClip as an alternative strategy in selected compromised patients with advanced HF before transplant. Patients with advanced HF comprise an estimated 1% to 10% of the overall HF population, and the prevalence is increasing because of the growing number of patients with HF and their better treatment and survival.<sup>15–17</sup> This is a clinical area where conventional treatments (i.e., guideline-directed drugs, percutaneous devices, conventional surgery) are often insufficient in reducing a patient's symptoms, and advanced (e.g., cardiac transplantation, mechanical cardiac support) or palliative therapies (e.g., inotropic infusions, ultrafiltration or peritoneal dialysis to control volume, or end-of-life comfort care) are needed.<sup>3</sup> However, in situations where a patient's clinical condition deteriorates or end-organ function is compromised, short-term therapies may be needed until mechanical cardiac support can be implanted or while the patient is waiting on the transplant list. The possible role of MitraClip as a bridge to transplant has already been reported in some case reports and limited case series.<sup>5–10</sup> The MitraBridge registry results can be considered as a proof of concept in a larger and more geographically diverse cohort of patients demonstrating the effective role of MitraClip as a bridge strategy to HTx in patients with advanced HF who are on the waiting list or at that moment not eligible or at high risk for HTx. In the MitraBridge population, the MitraClip procedure was followed by a sustained reduction of pulmonary hypertension in 34% of patients (defined as a reduction in sPAP by at least 10 mm Hg of baseline), allowing some of them to become eligible for HTx. Moreover, about 60.5% of patients were at least 1 NYHA functional class lower than baseline, in line with previous results on functional MR populations.<sup>18</sup> These findings may be a consequence of the increase in antegrade cardiac output and the decrease of left

ventricle filling pressure following mechanical reduction of MR.<sup>19</sup> In this series, all-cause mortality rate at 1 year was 4.5% and was lower compared with the 13% 1-year mortality rate reported by the Eurotransplant waiting list in 2019.<sup>1</sup>

In the near future, it would be desirable to have further data from observational studies regarding acute percutaneous MR repair in patients with cardiogenic shock and end-organ damage.<sup>20</sup> These data would allow us to evaluate whether percutaneous mitral valve interventions (with MitraClip and other mitral valve repair systems) could stabilize patients' hemodynamics and end-organ perfusion, allowing subsequent evaluation of patients' candidacy for HTx.

INTERMACS profiles could help to identify potential candidates for MitraClip in a bridge strategy. These profiles are commonly used as descriptors of disease severity in patients receiving mechanical circulatory support, and lately their utility in risk assessment and triaging of ambulatory patients with advanced HF was shown.<sup>21</sup> Most of the patients treated in this series were in INTERMACS profile  $\geq 3$ . INTERMACS profiles 1 (critical cardiogenic shock) and 2 (progressive decline despite inotropic support) identify patients that may be treated with either paracorporeal or percutaneous short-term ventricular assist devices as a BTD.<sup>3</sup> Although INTERMACS profiles alone are insufficient to evaluate an individual patient for urgent HTx or mechanical cardiac support, based on these preliminary data, selected INTERMACS profile  $\geq 3$  can be evaluated for MitraClip bridge strategy in patients with advanced HF and concomitant significant secondary MR.

Finally, about 80% of patients included in the MitraBridge registry would have been formally ineligible for the MitraClip procedure based on the COAPT trial criteria.<sup>22</sup> Conversely, MitraBridge patients are more similar to those from the Mitra-FR trial<sup>23</sup> because of extremely dilated left ventricles (median LVEDVi: 122.5 ml/m<sup>2</sup>) and proportionate<sup>24</sup> functional MR, according to available EROA (30 mm<sup>2</sup>) and RVol (41 ml/beat) values. Nevertheless, a higher success in reducing HF rehospitalizations was observed (rates of HF rehospitalizations at 1 year: MitraBridge 30%



vs Mitra-FR 48.7%), likely because of the clinical potential of MitraClip treatment when applied on top of guideline-directed medical therapy in a much younger population.

These findings can be helpful in improving indications, patient selection, and decision-making criteria for MitraClip use in patients with advanced HF and concomitant significant MR waiting for HTx.<sup>25,26</sup> In particular, patients with indication to BTd or to candidacy, who currently have few therapeutic options besides medical therapy alone, could benefit the most from this strategy.

## Study limitations

This study has several limitations. First, it is an observational study without a control group. Second, this is a real-world registry reporting the clinical practice in different centers and countries; therefore, echocardiographic and clinical outcomes have been reported by the different sites and investigators without core lab adjudication. In addition, the semi-quantitative MR grading evaluation for most patients (75.5%) represents an important methodological limitation. This reflects practice 2 years ago, well before the results of the COAPT trial,<sup>22</sup> which highlighted the importance of quantitative MR grading and pushed toward a greater clinical application of EROA and RVol. Third, the sample size remains relatively small. Fourth, a significant confounder in the comparison between hospitalization for HF before and after index procedure can exist, as those patients who underwent MitraClip would likely have closer medical follow-up after the procedure compared with the pre-procedure time. Finally, we want to underline the fact that this study is in a specific set of patients with advanced HF and concomitant significant MR, who have been chosen to undergo MitraClip procedure because of the favorable anatomical and clinical characteristics. Therefore, careful patient selection for this treatment strategy is of paramount importance, and the results should be interpreted with some caution. The conclusions should be considered exploratory, as generating hypotheses, and need to be confirmed in the future in a larger cohort of patients.

## Conclusions

In this cohort of patients with advanced HF with significant secondary MR who were either listed for transplantation, awaiting listing for transplantation, or in a decision toward candidacy for transplantation, the selected use of MitraClip as a bridge strategy to HTx was safe, with two thirds of patients free from adverse events at 1 year. These findings will serve to guide further study for MitraClip use in this high-risk population, which is needed to confirm this exploratory experience.

## Disclosure statement

Dr Rodrigo Estévez-Loureiro reports receiving grants and personal fees from Abbott during the conduct of the study.

The remaining authors have no conflicts of interest to declare.

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### 10.3. Anexo 3

2-year outcomes of MitraClip as a bridge to heart transplantation: The international MitraBridge registry.

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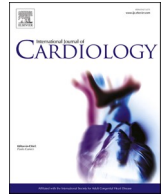
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journal homepage: [www.elsevier.com/locate/ijcard](http://www.elsevier.com/locate/ijcard)2-year outcomes of MitraClip as a bridge to heart transplantation: The international MitraBridge registry<sup>☆</sup>

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## ABSTRACT

**Background:** In the first report from the MitraBridge registry, MitraClip as a bridge to heart transplantation (HTx) proved to be at 1-year an effective treatment strategy for 119 patients with advanced heart failure (HF) who were potential candidates for HTx. We aimed to determine if benefits of MitraClip procedure as a bridge-to-transplant persist up to 2-years.

**Methods:** By the end of the enrollment period, a total of 153 advanced HF patients (median age 59 years, left ventricular ejection fraction  $26.9 \pm 7.7\%$ ) with significant secondary mitral regurgitation, who were potential candidates for HTx and were treated with MitraClip as a bridge-to-transplant strategy, were included in the MitraBridge registry. The primary endpoint was the 2-year composite adverse events rate of all-cause death, first hospitalization for HF, urgent HTx or LVAD implantation.

**Results:** Procedural success was achieved in 89.5% of cases. Thirty-day mortality was 0%. At 2-year, Kaplan-Meier estimates of freedom from primary endpoint was 47%. Through 24 months, the annualized rate of HF rehospitalization per patient-year was 44%. After an overall median follow-up time of 26 (9–52) months, elective HTx was successfully performed in 30 cases (21%), 19 patients (13.5%) maintained or obtained the eligibility for transplant, and 32 patients (22.5%) no longer had an indication for HTx because of significant clinical improvement.

**Conclusions:** After 2-years of follow-up, the use of MitraClip as a bridge-to-transplant was confirmed as an effective strategy, allowing elective HTx or eligibility for transplant in one third of patients, and no more need for transplantation in 22.5% of cases.

## 1. Introduction

The prevalence of advanced heart failure (HF) is increasing worldwide, due to the growing global number of HF patients and the improvement in their treatment and survival [1]. Even though the progression in advanced pharmacological and mechanical therapies has partly ameliorated the morbidity and mortality of these patients [2,3], prognosis remains poor, with a 1-year mortality ranging from 25 to 75% [2,4]. Heart transplantation (HTx) remains the only treatment option with effective mid- and long-term results, with a post-transplant 1-year survival of around 90% and a median survival of 12.5 years [4]. However, its accessibility is limited by recipient eligibility and organ donor scarcity [1,2]. As a consequence, advanced HF patients who are potential candidates for HTx, often need bridging therapies to reduce or reverse worsening and progression of underlying disease until a transplantable organ become available. Previously, 1-year results from the MitraBridge registry reported on the potential role of transcatheter edge-to-edge repair (TEER) with the MitraClip system as a bridge strategy to HTx in 119 patients with advanced HF<sup>5</sup>. Moderate or severe secondary mitral regurgitation (MR) is indeed a common finding in patients with HF<sup>6</sup>, which negatively affects their prognosis increasing the rate of admission for HF and the risk of mortality [7].

In the MitraBridge study, correction of significant secondary MR by TEER resulted to be a safe and effective procedure in advanced HF patients who were potential candidates or were waiting for HTx: procedural success of TEER was 87.5%, no death occurred at 30 days, and the procedure guaranteeing safe access to or eligibility for transplant in >30% of cases [5]. The present report aims to describe clinical outcomes of a larger series of patients with advanced HF post TEER up to 2-year of follow-up.

## 2. Methods

## 2.1. Registry design

The MitraBridge is an observational, international, multicenter registry created in 2018 and concluded in November 2021. The registry design and 1-year interim results were previously published [5]. In brief, all consecutive patients with chronic advanced HF (defined as New York Heart Association [NYHA] III or IV and/or left ventricular ejection fraction [LVEF]  $\leq 30\%$  and according to the definitions proposed by the Heart Failure Association of the European Society of Cardiology [8]) and concomitant moderate-to-severe or severe secondary MR, who were potential candidates for HTx and treated with MitraClip in the context of

a pre-specified bridge strategy, were evaluated for inclusion. By the end of the enrollment period, a total of 20 centers from Europe and Canada (3 more than that previously included [5]) have contributed to the registry. For the purpose of the present analysis, prolonged follow-up data of patients enrolled in the registry were requested and collected from each center whenever available.

The inclusion of patients in the study was approved at each institution by a local ethical committee or per local practice for the collection of prospective data. This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04293575) (NCT04293575).

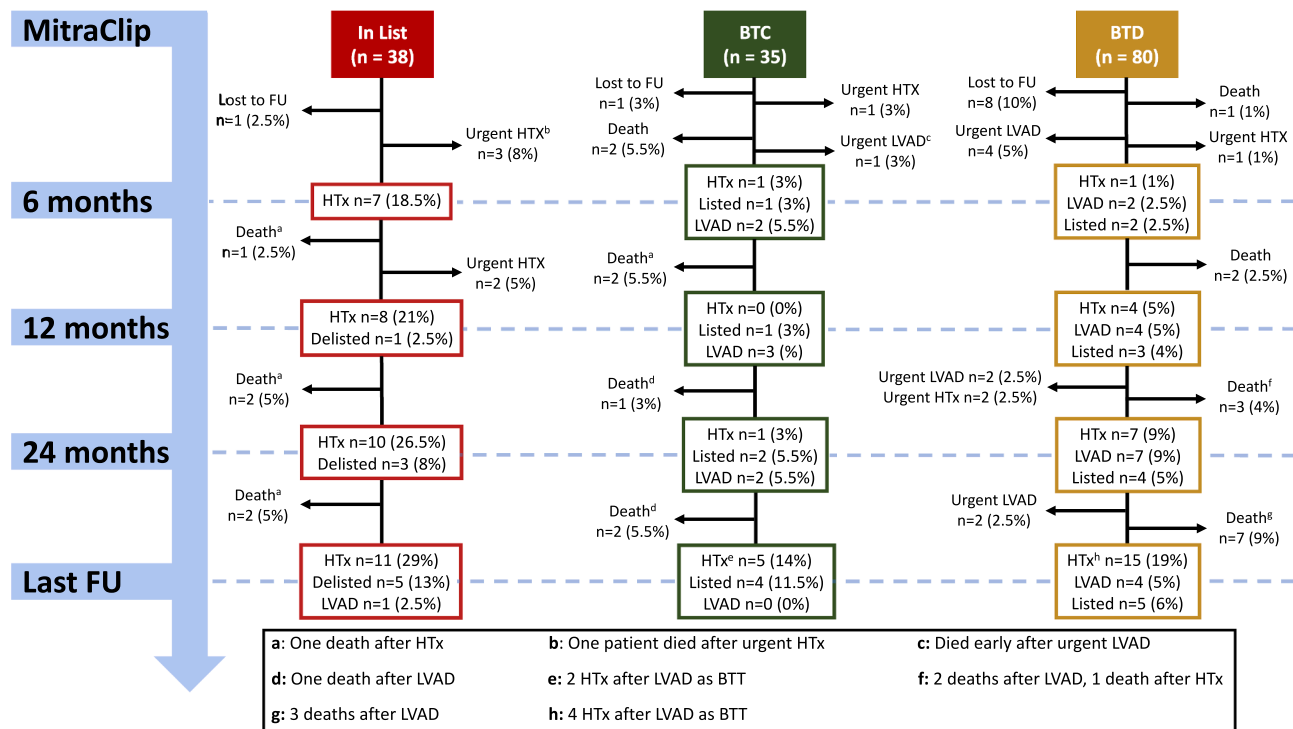
## 2.2. Patients selection

All potential candidates for HTx treated with MitraClip in the context of a pre-specified bridge strategy as per local Heart Team decision, were classified according to one of the following clinical conditions present at the time of the procedure:

1. patients active on an HTx waiting list (*In List group*) with a low likelihood to receive an organ rapidly (e.g., for low priority status) and/or progressive unstable clinical conditions;
2. patients with new unexpected clinical worsening and/or new history of acute HF decompensation, who were otherwise suitable for HTx (according to local Heart Team evaluation) but were still waiting for final clinical decision (*bridge to decision* [BTD] *group*);
3. patients who could not be yet listed for HTx (*bridge to candidacy* [BTC] *group*) because of concomitant, potentially reversible clinical contraindications or other reasons preventing eligibility to transplant.

## 2.3. Outcomes

The primary end-point of the present analyses was the 2-year composite adverse events rate of all-cause death, urgent HTx or left ventricular assist device (LVAD) implantation, and first rehospitalization for HF. The secondary end-point was the 2-year rate of first rehospitalization for HF. As exploratory outcome, we considered all HF rehospitalization within 24 months from MitraClip procedure, including recurrent events for patients with more than one hospitalization. Finally, the clinical status of patients at the time of last available follow-up was reported, in order to describe the rates of patients entering (or remaining) in the transplant waiting list, having no more indication to HTx because of significant echocardiographic and/or clinical improvements during the entire observational period, and going for elective HTx. When



**Fig. 1.** Timeline reporting relevant events during follow-up stratified according to pre-defined baseline criteria.

Data are presented as absolute numbers (percentages). HTx and LVAD refer to elective heart transplantation and elective LVAD implantation, respectively. Urgent HTx and urgent LVAD refer to urgent heart transplantation and urgent LVAD implantation, respectively.

Delisted identifies those patients who were removed from HTx waiting list. Listed identifies those patients who were included in HTx waiting list.

Median follow-up (25th and 75th percentiles) time: 26 (9–52) months; in 50.5% of cases a follow-up time of >2 years was available.

BTC = bridge to candidacy; BTD = bridge to decision; BTT = bridge to transplant; FU = follow-up; HTx = heart transplantation; LVAD = left ventricular assist device.

primary, secondary and exploratory outcomes were assessed, for patients who underwent LVAD implantation or HTx, follow-up data were censored at the time of these events.

#### 2.4. Statistical analysis

Results are presented as mean  $\pm$  SD for continuous variables normally distributed (tested by the Shapiro-Wilk normality test), as median (25th and 75th percentiles) for continuous variables without normal distribution, and as absolute numbers (percentages) for categorical data. One-way analysis of variance and Student's unpaired *t*-test were used to compare normally distributed continuous variables. For non-normally distributed continuous variables, the Kruskal-Wallis test and Wilcoxon rank-sum test were used to compare data between 3 or 2 groups, respectively. Chi-square and Fisher exact tests were used to compare categorical variables. Student's paired *t*-test and Wilcoxon matched-pairs signed-ranks test were used to compare mean changes from baseline to follow-up in normally distributed and non-normally distributed continuous echocardiographic variables, respectively. Event rates of primary composite and secondary (first rehospitalization for HF) endpoints were estimated using the Kaplan–Meier method; comparisons were performed using the log-rank test. The rate of rehospitalization for HF per patient-year (exploratory outcome) was calculated as the total number of HF hospitalization events divided by total follow-up years. Finally, association between MR severity at follow-up and study endpoints was investigated using univariate and multivariate (adjusting hazard ratio of MR severity for previously identified predictors of primary endpoints: HF hospitalization within previous 6 months, procedural failure, INTERMACS profiles 1–4, left ventricular ejection fraction, NYHA functional class IV<sup>5</sup>) cox regression analyses.

The statistical analysis, the Kaplan–Meier mortality curves, and the graphs were performed with the use of Stata version 14 (StataCorp LLC,

College Station, TX) and GraphPad Prism software version 6 (GraphPad, Inc., San Diego, CA).

### 3. Results

#### 3.1. Study population and procedural results

By the end of the enrollment period, further 34 advanced HF patients were screened and included in the MitraBridge registry, obtaining a final study population of 153 patients (median age 59 [53–63] years, 113 [74%] men). As previously reported [5], before MitraClip procedure, all patients were on guideline-directed medical therapy as tolerated, Supplementary Table 1. Nevertheless, HF symptoms were reported in all of them, with 93% of patients being classified in NYHA functional class III or IV. Moreover, at least one hospitalization for HF in the 6 months before the index procedure occurred in 63% of cases. According to the INTERMACS classification, large part of the study population was in profiles 3 to 6 (profiles 3–4 36%, profiles 5–6 47.5%), Supplementary Table 1.

At the time of MitraClip intervention, 38 patients (25%) were on the active HTx waiting list (In List group), 80 patients (52%) were still waiting for a final clinical decision (BTD group), while 35 patients (23%) could not be yet included in the transplant waiting list because of concomitant, potentially reversible contraindications (BTC group). Clinical conditions of patients belonging to the In List and BTC groups were previously described [5]. Supplementary Table 1 summarizes baseline characteristics of the overall population and of each study group.

As per inclusion study criteria, all patients had secondary MR: the severity of valve regurgitation was moderate-to-severe and severe in 15 (10%) and 138 (90%) cases, respectively. Mean left ventricular ejection fraction (LVEF) was  $26.9 \pm 7.7\%$ , with 107 patients (70%) having



values  $\leq 30\%$ . Adverse left chamber remodeling was reported in the majority of patients, with a median left ventricular end diastolic volume index of 119.8 (99–150.6) mL/m<sup>2</sup>. At baseline echocardiographic evaluation, elevated systolic pulmonary artery pressure (PAP,  $\geq 35$  mmHg) was reported in 136 patients (89%), with a median value of 50 (40–60) mmHg, Supplementary Table 2. Baseline right heart catheterization data were available for 112 (73%) patients: the hemodynamic evaluation confirmed the severity of left ventricular dysfunction (median cardiac index 1.9 [1.7–2.3] L/min/m<sup>2</sup>) and the elevated values of PAP (mean PAP  $33 \pm 10$  mmHg); 87.5% of patients had pulmonary hypertension, with a mean value of pulmonary arterial wedge pressure of  $24.6 \pm 9.5$  mmHg. Combined pre- and post-capillary pulmonary hypertension was reported in 61% of cases, Supplementary Table 2.

Procedural success according to the Mitral Valve Academic Research Consortium definition [9] was achieved in 89.5% of cases, with a higher rate of success for patients belonging to In List (92%) and BTB groups (93.5%) than to BTC group (77%;  $p = 0.023$ ), Supplementary Table 1. For three patients (2 from the In List group and 1 from the BTB group) no clip was implanted because of inadequate clip positioning (2 cases) and hemodynamic instability during the procedure (1 case). No deaths occurred during the procedure and within 30 days.

### 3.2. Clinical follow-up status

#### 3.2.1. Overall

The clinical follow-up was available for 143 patients (93.5%), with an overall median follow-up time of 26 (9–52) months; a follow-up time of  $>2$  years was available in 77 cases [55.5%, 50 (33–65) months]. All major events stratified according to each study group are reported in a chronological manner in Fig. 1. After MitraClip procedure, 13 deaths (9.1% of the entire study population with available follow-up) not related to HTx or LVAD occurred, in 9 cases secondary to a clear cardiovascular cause. 9 patients (6.5%) needed urgent LVAD implantation because of MitraClip bridge therapy failure with sudden clinical worsening. On the other hand, according to the progressive nature of their underlining disease, despite an initial hemodynamic stabilization after TEER, 17 patients (11.9%) underwent elective LVAD implantation after a median time of 15 (6–26) months: in 14 cases LVAD was positioned as bridge to HTx strategy; 3 patients received long-term mechanical circulatory support as destination therapy. Of these 26 patients who underwent urgent or elective LVAD implantation, 8 patients (31%) died after a median time of 398.5 (116–796.5) days, while in 6 cases (23.1%) elective HTx was performed after 777 (135–1001) days from LVAD positioning.

While 9 patients (6.5%) needed urgent HTx secondary to sudden clinical worsening despite MitraClip treatment, HTx according to standard listing criteria was successfully performed in 30 patients (21%) after a median time of 15 (5–29) months from the index procedure. Clinical follow-up after transplant was available in 22 of 39 cases (median time 376.6 (110–1022) days): 6 patients died after 11 (1–305) days from HTx because of acute organ rejection or infective complications; the other 16 patients were in good clinical conditions, in the absence of HF symptoms (NYHA functional class I).

Finally, a total of 32 patients (22.5%) no longer had an indication for HTx because of significant clinical improvement, Supplementary Table 3.

#### 3.2.2. In list group

Of the 38 patients included into the In list group, follow-up data were available in 37 cases (97.4%). Of these, after MitraClip procedure, 2 patients (5.5%) died, one patient (2.7%) needed elective LVAD implantation, 5 subjects (13.5%) received urgent HTx, while in 14 cases (37.8%) HTx according to standard listing criteria was performed. Until the last available follow-up contact, whereas 10 patients (27%) remained in list for HTx, 5 patients (13.5%) were delisted because of improvement of their clinical and echocardiographic conditions.

**Table 1**

2-year clinical outcomes.

| Outcomes                             | Overall<br>(n = 153) | In List<br>(n = 38) | BTB<br>(n = 80) | BTC<br>(n = 35) | p value <sup>a</sup> |
|--------------------------------------|----------------------|---------------------|-----------------|-----------------|----------------------|
| Primary Endpoint                     | 64 (53)              | 19 (61)             | 29 (50)         | 16 (51.5)       | 0.632                |
| HF<br>rehospitalization <sup>b</sup> | 48 (45)              | 14 (50)             | 22 (43)         | 12 (44)         | 0.749                |
| All-cause death                      | 7 (6.5)              | 1 (7)               | 3 (5)           | 3 (10)          | 0.536                |
| Urgent LVAD                          | 7 (7)                | 0 (0)               | 6 (13)          | 1 (3)           | 0.123                |
| Urgent HTx                           | 9 (8)                | 5 (15.5)            | 3 (7)           | 1 (3.5)         | 0.093                |

Data are presented as absolute numbers (Kaplan-Meier estimates of events). BTC = bridge to candidacy; BTB = bridge to decision; HF = heart failure; HTx = heart transplantation; LVAD = left ventricular assist device.

<sup>a</sup> p-value referring to log-rank test.

<sup>b</sup> First HF rehospitalization.

#### 3.2.3. BTC group

For 34 (97.1%) of 35 patients included into the BTC group follow-up data were available. Of these, during the follow-up period, 4 patients (11.8%) died, 7 patients underwent LVAD implantation (20.6%, in one case urgent LVAD placement was performed), and 5 patients received HTx (14.7%, one urgent HTx). Until the last available follow-up contact, whereas in 4 cases (11.8%) eligibility for transplant was achieved and patients moved to the active HTx waiting list, 12 patients (35.3%) no longer had an indication for HTx because of significant clinical improvement.

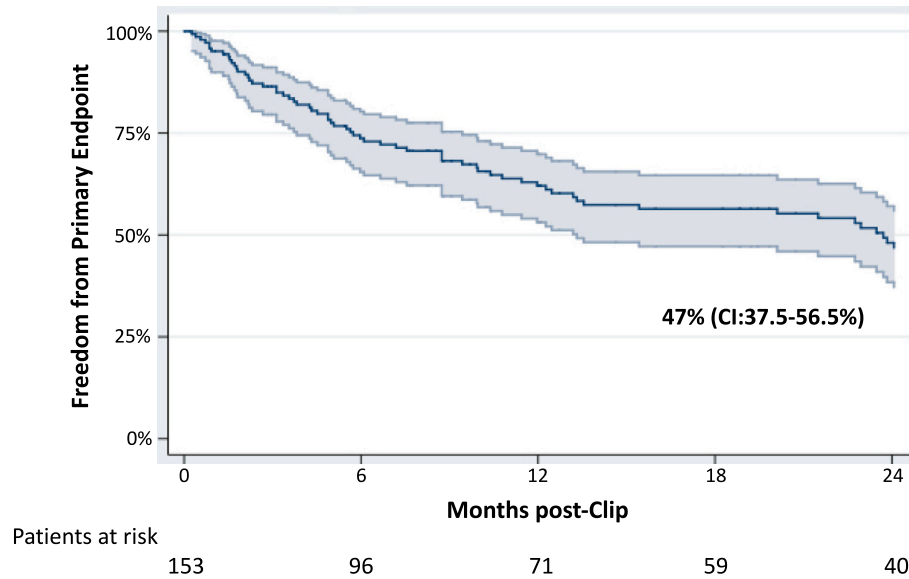
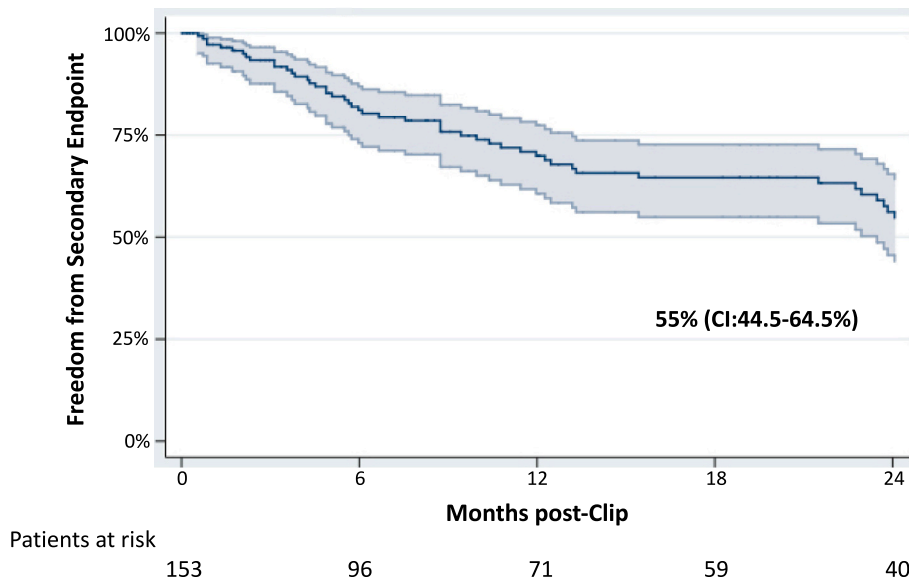
#### 3.2.4. BTB group

The clinical follow-up was available for 72 (90%) of the 80 patients included into the BTB group. After MitraClip procedure, 7 patients (9.7%) died, 18 patients underwent LVAD implantation (25%, 10 urgent LVAD placements), 15 patients received HTx (20.8%, 3 urgent HTxs). Until the last available follow-up contact, whereas 5 subjects (6.9%) achieved eligibility for transplant and moved to the active HTx waiting list, in 15 cases (20.8%) an indication for HTx was no longer needed because of significant clinical improvement.

### 3.3. Echocardiographic follow-up

Echocardiographic follow-up data before HTx or LVAD implantation were available in 119 cases (78%), with a median time to the last available echocardiographic control of 391 (211–631) days. A persistent significant improvement in MR severity was observed in most of the study population, with 69% of patients having a MR grade  $\leq 2+$ , Supplementary Fig. 1. MitraClip treatment prevented a further deterioration of left ventricular function and dimension, guaranteeing that values of LVEF and left ventricular end diastolic volume remained stable (LVEF baseline  $27.4 \pm 7.4\%$  vs follow-up  $26.5 \pm 8.7\%$ ,  $p$ -value = 0.166; left ventricular end diastolic volume baseline 220 [181.8–278] mL vs follow-up 239 [170.5–272.5] mL,  $p$ -value = 0.979). A significant amelioration in pulmonary hemodynamics was also reported, with a reduction in systolic PAP from 50 (40–61) mmHg to 43 (33–53) mmHg,  $p$ -value  $< 0.001$ . Finally, no deterioration of right ventricular function occurred (tricuspid annular plane systolic excursion baseline  $17.4 \pm 4$  mm vs follow-up  $17.7 \pm 4.1$  mm,  $p$ -value = 0.492), Supplementary Fig. 2. For those patients who no longer had an indication for HTx, at echocardiographic follow-up evaluation (data available for 31 of 32 patients) MR severity  $\leq 2+$  was reported in 80.5% of cases; the median values of left ventricular end diastolic volume and systolic PAP changed from 179 (143–229) mL to 170.45 (150–248) mL,  $p$ -value = 0.665, and from 45 (37.5–53) mmHg to 33 (25–42.5) mmHg,  $p$ -value  $< 0.001$ , respectively. Values of LVEF remained stable (from  $31.8 \pm 7.3\%$  to  $31.5 \pm 7.5\%$ ,  $p$ -value = 0.742).



**A****B**

**Fig. 2.** Kaplan-Meier curves of freedom from A) primary composite endpoint and from B) secondary endpoint.

Estimates rate of freedom from events with 95% confidence interval are shown.

HF = heart failure; HTx = heart transplantation; LVAD = left ventricular assist device.

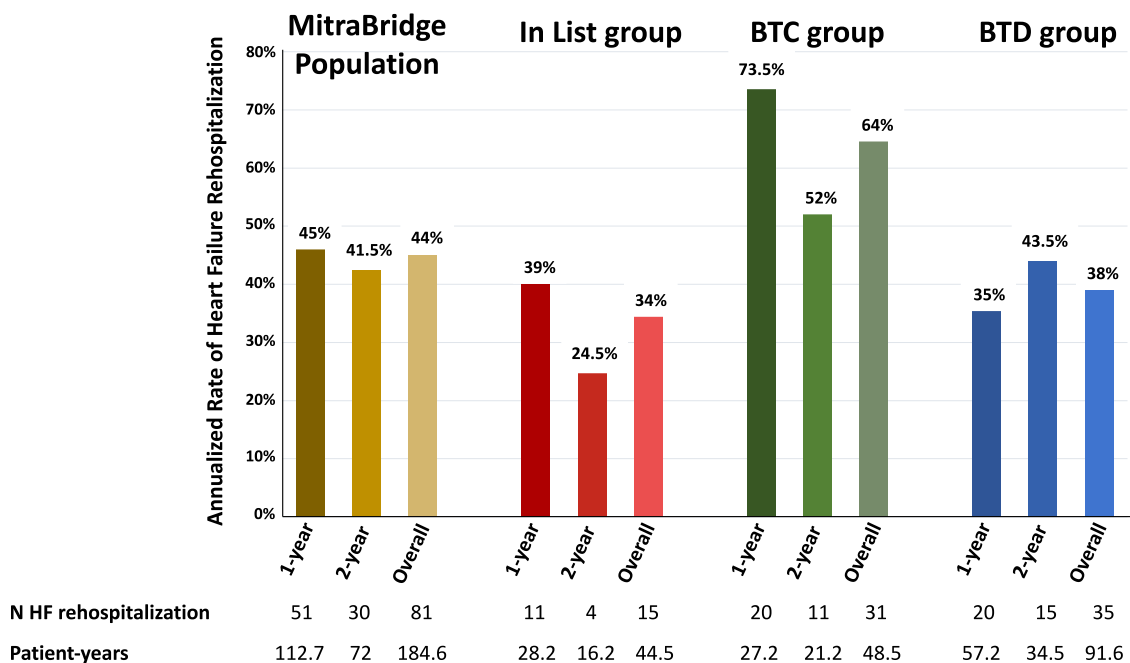
### 3.4. Clinical outcomes

The 2-year Kaplan-Meier estimates rate of primary composite endpoint (all-cause death, urgent HTx or LVAD implantation, and first rehospitalization for HF) was 53%. Within 24 months from MitraClip treatment, 7 all-cause deaths, 48 first rehospitalizations for HF, 9 urgent HTx, and 7 urgent LVAD implantations occurred, [Table 1](#), [Fig. 2A](#). The 2-year Kaplan-Meier estimates rate of first rehospitalization for HF (secondary endpoint) was 45%, [Table 1](#), [Fig. 2B](#). Through 24 months, the total number of HF hospitalization was 81, occurring in 48 patients, with

an annualized rate of events of 44% per patient-year, [Fig. 3](#). At univariate and multivariate cox regression analyses, having a MR severity at follow-up lower than moderate was identified as an independent predictor of freedom from primary and secondary endpoint, [Fig. 4](#).

### 4. Discussion

Considering all patients included in the MitraBridge registry until the end of the enrollment period, and extending the follow-up period, MitraClip treatment was confirmed as an alternative effective “bridge



**Fig. 3.** Exploratory outcome: annualized rate of HF rehospitalization.

Here reported annualized rate of HF hospitalization occurring in the first year, in the second year and within 2 years from MitraClip treatment. Recurrent events for patients with more than one hospitalization were considered.

BTC = bridge to candidacy; BTD = bridge to decision; HF = heart failure.

strategy” to HTx in a selected cohort of advanced HF patients with secondary MR. Indeed, the use of MitraClip as a bridge to transplant strategy allowed: 1) a 2-year estimates of freedom from composite adverse events (primary endpoint) of 47%, 2) safe access to HTx in 21% of patients, 3) to maintain or obtain the eligibility for transplant in 13.5% of cases, and 4) to rule out consideration for HTx because of clinical improvement in 22.5% of the study population.

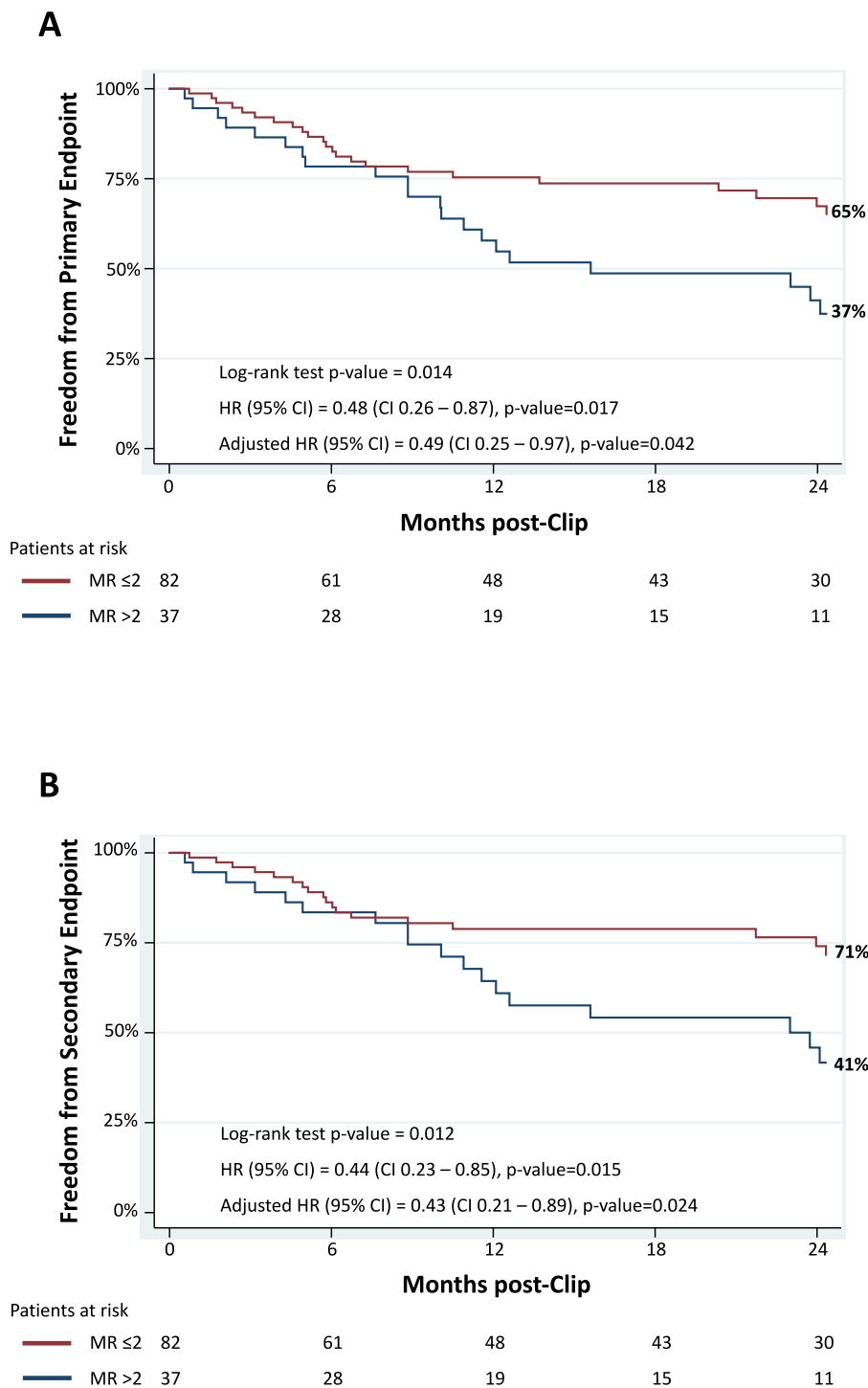
The prevalence of patients with advanced HF continues to rise, with an estimated number in the U.S. adult population ranging from 100,000 to 300,000 [1,10]. At this stage of HF, optimal medical therapy is insufficient to alleviate HF symptoms and prevent worsening of patient’s prognosis, and more advanced therapy are needed. HTx remains the best treatment option for these patients, with a post-transplant 1-year survival of around 90% and a median survival of 12.5 years [4,11]; nevertheless, its accessibility is limited by recipient eligibility and organ donor scarcity, with a difference between heart requests and organ donor availability of at least an order of magnitude [12]. Therefore, to prevent clinical deterioration and reduce waitlist mortality, potential candidates for HTx often need bridging therapies until a transplantable organ become available.

Limited data on the potential role of MitraClip treatment as a bridge to HTx have been previously published [13–18], and these evidences have been than confirmed by interim results from the larger cohort of patients included in the MitraBridge registry [5]. Secondary MR is indeed a common finding in advanced HF patients [6], which negatively affects their prognosis [7,19]; in these advanced stages of the disease, where volume overload and reduced stroke volume dominate the picture leading to persistent congestion and low-flow syndrome [10], a significant regurgitant volume might further increase left ventricular end-diastolic pressure and impair forward stroke volume. The MitraClip treatment, interrupting this vicious circle, might guarantee patients clinical and hemodynamic stabilization, and consequent safe access to HTx [20]. Extended results from the MitraBridge registry further confirm the present hypothesis. Up to 2-year from MitraClip procedure, TEER permitted to ameliorate patient’s clinical status and mitigate the frequency of HF rehospitalizations: through 24 months the annualized

rate of HF hospitalization was 44% per patient-year, which is greater than that observed in the device group of the COAPT trial (35.8%) [21], but far lower than that reported in the device group of the Mitra-FR trial (88.3%) [22]. According to the differences between the three populations, these results highlight the potential role of MitraClip treatment even in a more advanced setting than that considered in the COAPT trial [23], further supporting current guidelines recommendations which give a potential indication to TEER of MR even in patients who do not fulfil the COAPT inclusion criteria but who may benefit from this procedure to improve symptoms and as bridge to transplant [4].

As observed at echocardiographic follow-up control, TEER resulted in a significant improvement in pulmonary hemodynamics preventing the development of right ventricular dysfunction. In this advanced setting, severe post-capillary pulmonary hypertension is a common finding which ultimately leads to increased pulmonary vascular resistance and therefore patient’s ineligibility for HTx [18,24,27]. Moreover, a significant elevation in afterload might deteriorate right ventricular function leading to systemic venous congestion and consequent progressive multi-organ failure [25]. Correction of mitral regurgitation could reverse this maladaptive process as previously reported in some case reports and limited case series [16,18,26,28]. Even in the Mitra-Bridge population, a significant reduction in systolic PAP (baseline 50 [40–61] mmHg vs follow-up 43 [33–53] mmHg,  $p$ -value<0.001) was observed after MitraClip intervention, guaranteeing the preservation of right ventricular function. In particular, in 4 of 7 patients who could not be listed for HTx before MitraClip procedure because of severe pulmonary hypertension with elevated pulmonary vascular resistance, and for whom hemodynamics follow-up data were available, after 1 year a significant reduction in pulmonary vascular resistance was observed (baseline vs follow-up: patient n 1 = 5.81 vs 3.9 WU; patient n 2 = 4.44 vs 1.9 WU; patient n 3 = 15.97 vs 4.1 WU; patient n 4 = 6.49 vs 3 WU). The achievement of these results allowed patients to undergo elective HTx or to become eligible for transplant.

Durable mechanical circulatory support obtained through LVAD implantation represents an effective treatment to improve quality of life and extend survival of advanced HF patients [12]. Despite the promising



**Fig. 4.** Kaplan-Meier curves of freedom from A) primary and B) secondary endpoint stratified by follow-up mitral regurgitation severity.

Adjusted HR: HR of MR was adjusted for previously identified predictors of primary endpoints: HF hospitalization within previous 6 months, procedural failure, INTERMACS profiles 1–4, left ventricular ejection fraction, NYHA functional class IV<sup>5</sup>.

HR = hazard ratio; MR = mitral regurgitation; CI = confidence interval.

results of new devices [28], because of the poor long-term survival and the high frequency of adverse events, LVAD therapy is still restricted to a small portion of high-risk advanced HF patients (INTERMACS 1–3 [29,30]), leaving few therapeutic options for patients in INTERMACS profiles 4–7. In the MitraBridge registry, >80% of patients were in INTERMACS profile >3 before the index procedure. According to our results, TEER with the MitraClip system seems to be a suitable treatment strategy for these patients who have few chances to undergo early cardiac replacement therapy.

The present report from the MitraBridge registry is a further proof of

concept of the potential role of MitraClip treatment in this complex scenario. Larger prospective data are needed in order to confirm our findings and pave the way at extending indication for TEER even in a more advanced setting, where current criteria of positive response to treatment are not entirely satisfied [4,20].

#### 4.1. Study limitations

Our study has several limitations that have to be mentioned. First, this is an observational study without a control group. Second, this is a

real-world registry reporting the clinical practice in different centers and countries; therefore, echocardiographic and clinical outcomes have been reported by the different sites and investigators without core lab adjudication. Third, as long as we considered MitraClip interventions performed before January 2021, no patient was treated with SGLT-2 inhibitors for HF therapy optimization before the index procedure. Finally, the MitraBridge population includes a specific set of patients with advanced HF and concomitant significant secondary MR, who have been chosen to undergo MitraClip procedure because of the favourable anatomical and clinical characteristics. Therefore, careful patient selection for this treatment strategy is of paramount importance, and the results should be interpreted with some caution.

## 5. Conclusions

After two years of follow-up, the use of MitraClip as a bridge to transplant in a larger and selected cohort of advanced HF patients with significant secondary MR who were potential candidates for HTx, was confirmed to be an effective strategy, allowing elective HTx or eligibility for transplant in one third of patients, and no more need for transplantation because of significant clinical improvement in 22.5% of cases.

## Sources of funding or support

None.

## Declaration of Competing Interest

A.S. has served as a consultant and received consulting fees from NeoChord Inc.; R.E.L. received speaker fees from Abbott, Boston and Edwards; M.A. received speaker fees from Abbott Vascular and Medtronic; P.G. has been a proctor for Abbot; N.M.V.M. received research grant support from Abbott Vascular, Biotronik, Medtronic, Boston Scientific, Edwards Lifesciences, Daiichi Sankyo, Abiomed en PulseCath BV; F.S. received consultancy and lecture's fees from Abbott and Edwards.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2023.131139>.

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#### 10.4. Anexo 4

Conservative, Surgical and Percutaneous Treatment for Mitral Regurgitation shortly after Acute Myocardial Infarction.

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# Conservative, surgical, and percutaneous treatment for mitral regurgitation shortly after acute myocardial infarction

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## Aims

Severe mitral regurgitation (MR) following acute myocardial infarction (MI) is associated with high mortality rates and has inconclusive recommendations in clinical guidelines. We aimed to report the international experience of patients with secondary MR following acute MI and compare the outcomes of those treated conservatively, surgically, and percutaneously.

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† These authors contributed equally to this study.

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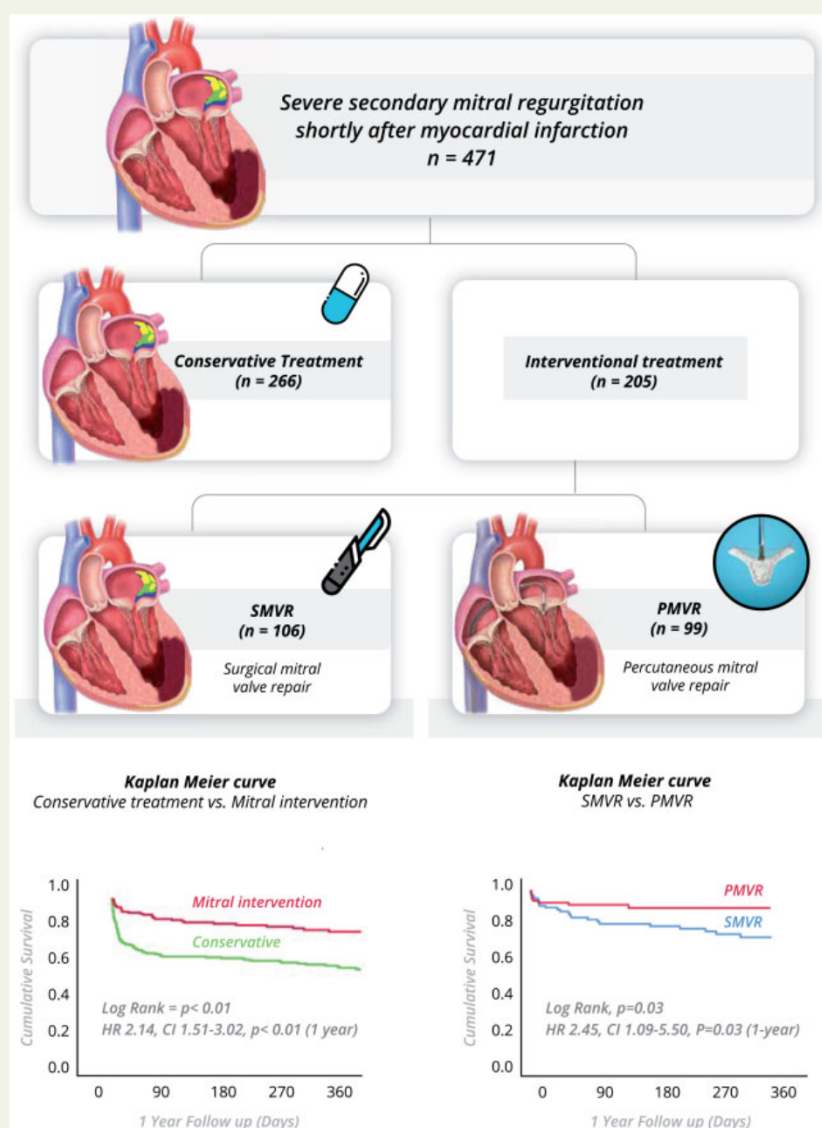
## Methods and results

Retrospective international registry of consecutive patients with at least moderate-to-severe MR following MI treated in 21 centres in North America, Europe, and the Middle East. The registry included patients treated conservatively and those having surgical mitral valve repair or replacement (SMVR) or percutaneous mitral valve repair (PMVR) using edge-to-edge repair. The primary endpoint was in-hospital mortality. A total of 471 patients were included (43% female, age  $73 \pm 11$  years): 205 underwent interventions, of whom 106 were SMVR and 99 PMVR. Patients who underwent mitral valve intervention were in a worse clinical state (Killip class  $\geq 3$  in 60% vs. 43%,  $P < 0.01$ ), but yet had lower in-hospital and 1-year mortality compared with those treated conservatively [11% vs. 27%,  $P < 0.01$  and 16% vs. 35%,  $P < 0.01$ ; adjusted hazard ratio (HR) 0.28, 95% confidence interval (CI) 0.18–0.46,  $P < 0.01$ ]. Surgical mitral valve repair or replacement was performed earlier than PMVR [median of 12 days from MI date (interquartile range 5–19) vs. 19 days (10–40),  $P < 0.01$ ]. The immediate procedural success did not differ between SMVR and PMVR (92% vs. 93%,  $P = 0.53$ ). However, in-hospital and 1-year mortality rates were significantly higher in SMVR than in PMVR (16% vs. 6%,  $P = 0.03$  and 31% vs. 17%,  $P = 0.04$ ; adjusted HR 3.75, 95% CI 1.55–9.07,  $P < 0.01$ ).

## Conclusions

Early intervention may mitigate the poor prognosis associated with conservative therapy in patients with post-MI MR. Percutaneous mitral valve repair can serve as an alternative for surgery in reducing MR for high-risk patients.

## Graphical Abstract



The registry included 471 patients with significant mitral regurgitation within 90-days after acute myocardial infarction who remained symptomatic on optimal medical therapy. Overall, patients who treated by mitral intervention had better survival over patients treated conservatively. Among patients treated with mitral intervention, Surgical mitral valve repair or replacement (SMVR) was associated with a higher mortality rate compared with percutaneous mitral valve repair (PMVR).



**Keywords**

Mitral regurgitation • Percutaneous edge-to-edge repair • Mitral valve surgery • Myocardial infarction

**Introduction**

Acute or sub-acute mitral regurgitation (MR) may develop in the setting of myocardial infarction (MI) as a result of papillary muscle rupture that requires urgent surgical intervention or due to the rapid remodelling of the infarcted left ventricle (LV) causing apical and inferior displacement of the papillary muscles that leads to secondary MR. It is often accompanied by haemodynamic instability and has been linked to poor prognosis.<sup>1-4</sup> The relatively acute onset of MR can lead to pulmonary oedema and even cardiogenic shock. Moderate or severe MR is found in 12% of all ST-elevation MI patients at 30-day follow-up.<sup>5</sup> Although even mild MR was associated with excess morbidity and mortality, patients who presented with moderate to severe or severe (+3 or +4) MR faced the worst outcomes with high mortality rates of 24%, 42%, and 52% at 30 days, 6 months, and 1 year, respectively.<sup>6</sup> These rates could be even higher among patients with acute decompensation that require mechanical ventilation, intravenous diuretics, intravenous inotropes, or mechanic circulatory support. Most of these patients are deemed as high risk for mitral valve surgery or even considered inoperable, and thus managed conservatively with a grim prognosis. Until recently, the only possible intervention targeting MR was surgery. However, in this setting, it is associated with high mortality rates early after MI, reaching 25%.<sup>7</sup>

Previous literature is limited to a small case series, reporting that percutaneous mitral valve repair (PMVR) using the MitraClip (Abbott; Menlo Park, CA, USA) device after MI complicated by severe MR, is safe and effective. Our group published two case series, showing that, in the majority of patients, salvage PMVR procedure significantly decreased MR and improved haemodynamic parameters, leading to rapid clinical improvement.<sup>8,9</sup> However, the descriptive data were not compared with any reference groups. To address this gap in knowledge, we aimed to collect the largest experience worldwide of acute MR following MI treated with PMVR and compare the characteristics and outcomes of such patients with patients treated surgically or conservatively.

**Methods**

The International Registry of MitraClip in Acute Mitral Regurgitation following acute Myocardial Infarction (IREMMI) was established to assess the safety and outcomes of patients who underwent PMVR in an acute setting following MI. We approached all participating centres to review the data of patients who developed symptomatic post-MI MR.

Our current study cohort included patients who had at least symptomatic MR grade +3 within 90 days after acute MI (both ST-elevation and non-ST-elevation) between December 2009 and March 2020, in 21 centres in North America, Europe, and the Middle East, which had been managed by the surgical mitral intervention (repair or replacement, SMVR), PMVR with the MitraClip system, or without intervention (conservative group). As patients with papillary muscle rupture have different

prognoses and are often treated with urgent surgical intervention, they were excluded from the analysis.

All participating centres are capable of performing both surgical and percutaneous mitral valve treatment based on multidisciplinary clinical team decisions. Medical care in intensive care units (intravenous diuretic, vasoactive medications, mechanical ventilation, and mechanical support devices) and decisions about treatment approaches were taken by a local multidisciplinary team and conducted based on clinical assessment.

All patients or their legal guardians provided written informed consent prior to the intervention. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and was approved by individual local ethics committees. Missing information in the dataset was resolved with the investigators after direct contact from registry personnel.

**Echocardiographic evaluation**

Routine echocardiographic exams were performed in all patients. The severity of MR, left ventricular ejection fraction (LVEF), systolic pulmonary artery pressure (sPAP), and mitral valve gradient was measured and graded according to the American Society of Echocardiography guidelines.<sup>10,11</sup> The severity of MR was assessed by integrated multiparametric visual evaluation tools in accordance with standard clinical practice (incorporating 2D, spectral, and colour Doppler images), using an ordinal scale (grading 0 no MR, 1+ mild MR, 2+ moderate MR, 3+ moderate-to-severe MR, 4+ severe MR). Significant MR was considered as grades 3+ and 4+. Mitral regurgitation mechanism was thoroughly evaluated and classified as primary mechanical papillary muscle rupture or secondary MR.

**Surgical mitral valve intervention**

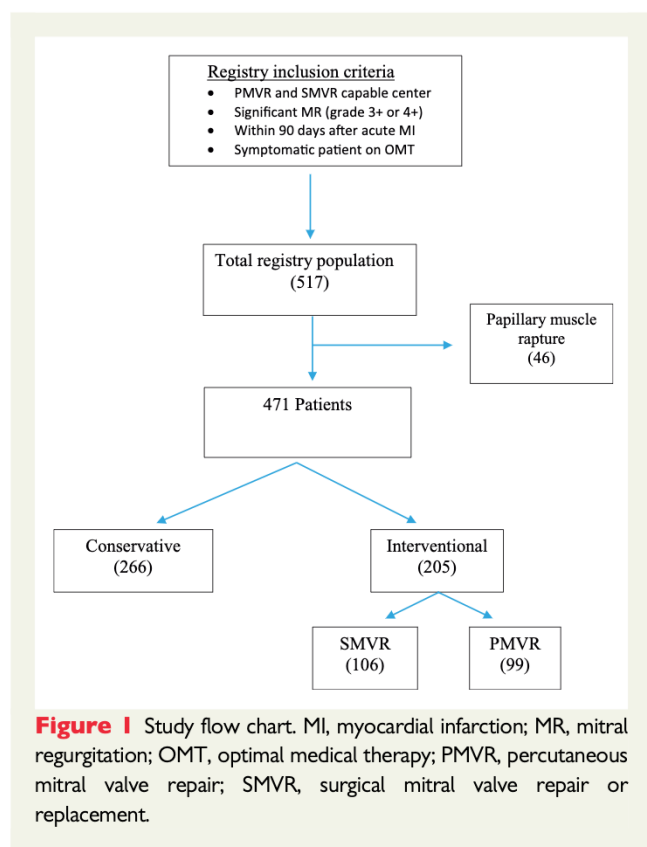
Mitral valve repair or replacement was performed under general anaesthesia in an operating theatre. Procedural success was defined as successful repair or replacement of the mitral valve with reduction of MR grade to  $\leq 2+$  and successful weaning from cardiopulmonary bypass.

**Percutaneous mitral valve intervention**

Percutaneous mitral valve intervention was performed using the MitraClip system. The procedure was performed under general anaesthesia, with fluoroscopy and transoesophageal echocardiography routinely used for guidance. The implantation procedure was performed as previously described.<sup>12</sup> Immediate procedural success was defined as successful reduction of MR grade to  $\leq 2+$ .

**Outcomes**

Procedural and clinical adverse events during follow-up were defined according to the Mitral Valve Academic Research Consortium (MVARC).<sup>13</sup> The primary outcome of this study was in-hospital all-cause mortality. Secondary endpoints were immediate procedural success, 1-year mortality, echocardiographic (MR grade and sPAP), and clinical [New York Heart Association (NYHA) class] outcomes. Safety outcomes included procedural and peri-procedural complications. Major procedural complications were defined as MI, stroke, cardiac tamponade, reintervention for adverse events or failed procedure, renal failure requiring renal replacement therapy, septicemia, or transfusion of two or more blood units after the procedure.



Clinical status was assessed using NYHA functional class.

Hospitalization duration was measured from index MI to discharge or in-hospital mortality.

## Statistical analysis

Our main analyses compared conservative vs. intervention approaches and SMVR vs. PMVR. We repeated the analysis after excluding patients who died in-hospital and in subgroups according to patients' median European System for Cardiac Operative Risk Evaluation (EUROSCORE II) to potentially generate additional insights.

Patient characteristics are reported according to variable properties. Categorical variables are reported as number (%), and differences between subgroups were tested using the  $\chi^2$  test or Fisher's exact test where appropriate. Continuous variables are reported according to their distribution. Those with a normal distribution are reported as mean ( $\pm$ standard deviation), and differences between subgroups were tested using Student's *t*-test. Those without a normal distribution are reported as median [interquartile range (IQR)], and differences between subgroups were tested using Mann–Whitney *U* test. A *P*-value  $<0.05$  was considered statistically significant.

Kaplan–Meier estimates were used to calculate survival curves, which were compared using the log-rank test. All clinical events were analysed by time to the first event for Kaplan–Meier analysis.

We performed a univariate and multivariable logistic regression method using backward elimination method (likelihood ratio was used as removal criteria) for the primary outcome, in-hospital mortality, using a myriad of clinically significant co-factors: age, gender, S/P MI, renal failure (grade 2+), anterior wall involvement, Killip class 3+, LVEF, and use of mechanical support device. The analysis was performed separately for

conservative vs. intervention groups and SMVR vs. PMVR. We used a univariate Cox regression model for 1-year mortality using potential predictors; those found to be significant in the univariate model were then included in a subsequent multivariable model.

To further validate our findings, we performed a propensity score matching to create two groups with similar baseline characteristics. The first propensity score was calculated as the probability of a patient to underwent intervention and the second propensity score to underwent PMVR. Propensity score was calculated using logistic regression. Based on theoretical knowledge, age, gender, body mass index, hypertension, diabetes, dyslipidaemia, chronic obstructive pulmonary disease, prior stroke, chronic kidney disease—grade 2+, multivessel coronary artery disease, EuroSCORE II, ST-elevation MI presentation, Killip class  $>3$ , LVEF, cardiogenic shock, vasoactive medication, and use of any mechanical support device were included in the multivariable logistic regression. For matching SMVR vs. PMVR, the same set of parameters were used not including prior MI, prior coronary artery bypass grafting (CABG) and percutaneous coronary intervention in the balancing analysis due to inherent differences.

The matching ratios for the treatment groups were 1:1. After matching, both groups were confirmed to be similar in baseline characteristics using absolute standardized mean difference (SMD). Absolute SMD  $<0.1$  was considered as neglect difference.

In-hospital mortality was compared between groups using McNemar's test or Fisher's exact test if not applicable. Stratified Cox regression was used to study the association between type of treatment and 1-year mortality. The IBM Statistical Package for the Social Sciences (SPSS) Statistics 26.0 (IBM Corp., Armonk, NY, USA) was utilized to perform the analyses.

## Results

After excluding 46 patients who had papillary muscle rapture, the final study cohort included 471 patients with significant secondary MR shortly after MI. Two hundred and sixty-six patients were treated conservatively, and 205 underwent mitral valve interventions (SMVR or PMVR) (Figure 1). The median follow-up was 239 days (IQR 42–418).

The mean age was  $73 \pm 11$  years, 43% were female, 38% had diabetes mellitus, and 26% had previous MI. Overall, patients in the conservative management group were older compared with patients who underwent mitral valve intervention ( $75 \pm 12$  vs.  $70 \pm 10$  years,  $P < 0.01$ ). Patients in the intervention group had higher rates of multivessel coronary artery disease (77% vs. 65%,  $P = 0.02$ ), previous MI (34% vs. 20%,  $P < 0.01$ ), and were more likely to present with cardiogenic shock (41% vs. 30%,  $P = 0.01$ ). Anterior wall involvement was not significantly different between the conservative and intervention groups (37% vs. 28%,  $P = 0.08$ ). Ultimately, the surgical risk was higher in the intervention group [EUROSCORE II of 10% (IQR 5–19) vs. 8% (IQR 3–16),  $P < 0.01$ ]. Baseline characteristics are presented in Table 1.

## Intervention: surgical mitral valve repair or replacement and percutaneous mitral valve repair

A total of 106 patients were treated with SMVR and 99 were treated with PMVR. Patients treated with PMVR were older ( $71 \pm 10$  vs.  $68 \pm 10$ ,  $P = 0.03$ ), had a higher prevalence of previous cardiac events,

**Table 1** Baseline patient characteristics in the Conservative and Intervention groups (SMVR and PMVR)

| Variable               | Conservative group<br>(n = 266) | Intervention group<br>(n = 205) | P-value         | SMVR<br>(n = 106) | PMVR<br>(n = 99) | P-value         |
|------------------------|---------------------------------|---------------------------------|-----------------|-------------------|------------------|-----------------|
| Age, years             | 75 ± 12                         | 70 ± 10                         | <b>&lt;0.01</b> | 68 ± 10           | 71 ± 10          | <b>0.03</b>     |
| Female sex             | 124 (47)                        | 79 (39)                         | 0.09            | 28 (26)           | 51 (51)          | <b>&lt;0.01</b> |
| BMI, kg/m <sup>2</sup> | 27 ± 4                          | 27 ± 5                          | 0.98            | 27 ± 4            | 26 ± 5           | 0.33            |
| Hypertension           | 197 (74)                        | 137 (67)                        | 0.10            | 67 (63)           | 70 (71)          | 0.30            |
| Diabetes               | 97 (36)                         | 83 (40)                         | 0.39            | 36 (34)           | 47 (47)          | 0.06            |
| Dyslipidaemia          | 122 (46)                        | 124 (60)                        | <b>0.02</b>     | 59 (56)           | 65 (66)          | 0.16            |
| COPD                   | 17 (6)                          | 25 (12)                         | <b>0.03</b>     | 9 (8)             | 16 (16)          | 0.13            |
| Prior stroke           | 15 (6)                          | 18 (9)                          | 0.20            | 6 (6)             | 12 (12)          | 0.14            |
| CKD grade ≥2           | 82 (31)                         | 43 (24)                         | <b>0.03</b>     | 13 (12)           | 30 (30)          | <b>0.01</b>     |
| Multivessel CAD        | 174 (65)                        | 158 (77)                        | <b>0.02</b>     | 78 (74)           | 80 (81)          | 0.25            |
| Prior MI               | 52 (20)                         | 70 (34)                         | <b>&lt;0.01</b> | 15 (14)           | 55 (56)          | <b>&lt;0.01</b> |
| Prior CABG             | 19 (7)                          | 29 (12)                         | <b>0.01</b>     | 1 (<1%)           | 28 (27)          | <b>&lt;0.01</b> |
| EuroSCORE II, %        | 8 [3–16]                        | 10 [5–19]                       | <b>&lt;0.01</b> | 10 [5–16]         | 10 [7–21]        | <b>0.03</b>     |
| STEMI presentation     | 161 (61)                        | 116 (57)                        | 0.40            | 45 (42)           | 71 (72)          | <b>&lt;0.01</b> |
| Involved wall—anterior | 97 (37)                         | 58 (28)                         | 0.08            | 22 (21)           | 35 (36)          | <b>0.02</b>     |
| PCI                    | 199 (75)                        | 131 (65)                        | <b>0.02</b>     | 37 (35)           | 94 (94)          | <b>&lt;0.01</b> |
| Killip class ≥3        | 114 (43)                        | 123 (60)                        | <b>&lt;0.01</b> | 57 (54)           | 66 (67)          | 0.07            |
| MR grade 4+            | 124 (47)                        | 150 (73)                        | <b>&lt;0.01</b> | 70 (66)           | 80 (81)          | <b>0.02</b>     |
| sPAP, mmHg             | 40 ± 17                         | 47 ± 19                         | <b>&lt;0.01</b> | 40 ± 17           | 54 ± 19          | <b>&lt;0.01</b> |
| LVEF, %                | 40 ± 12                         | 40 ± 11                         | 0.95            | 45 ± 10           | 35 ± 11          | <b>&lt;0.01</b> |
| Cardiogenic shock      | 79 (30)                         | 84 (41)                         | <b>0.01</b>     | 33 (31)           | 51 (52)          | <b>&lt;0.01</b> |
| Mechanical ventilation | 47 (18)                         | 65 (33)                         | <b>&lt;0.01</b> | 26 (25)           | 39 (39)          | 0.07            |
| Vasoactive medication  | 86 (33)                         | 84 (43)                         | <b>0.05</b>     | 45 (43)           | 39 (39)          | 0.39            |
| IABP                   | 35 (13)                         | 77 (38)                         | <b>&lt;0.01</b> | 44 (47)           | 33 (33)          | 0.25            |
| ECMO                   | 0 (0)                           | 5 (2)                           |                 | 0 (0)             | 5 (5)            |                 |
| MCS                    | 36 (14)                         | 78 (38)                         | <b>&lt;0.01</b> | 44 (42)           | 34 (34)          | 0.32            |

Values are given as mean ± standard deviation, n (%), or median [interquartile range].

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MSD, mechanical circulatory support; PCI, percutaneous coronary intervention; PMVR, percutaneous mitral valve repair; sPAP, systolic pulmonary artery pressure; SMVR, surgical mitral valve repair or replacement; STEMI, ST-elevation myocardial infarction.

Values in bold are statistically significant p-values.

history of prior MI (56% vs. 14%,  $P < 0.01$ ), and prior CABG (27% vs. 1%,  $P < 0.01$ ), compared with patients that underwent surgery. Furthermore, patients treated with PMVR were more likely to present in severe clinical condition; 52% of them had a cardiogenic shock, compared with 31% in the surgical group ( $P < 0.01$ ), had a significantly lower LVEF ( $35\% \pm 11\%$  vs.  $45\% \pm 10\%$ ,  $P < 0.01$ ) and higher anterior wall involvement (36% vs. 21%,  $P = 0.02$ ) (Table 1). Of those treated surgically, 60 (57%) underwent mitral valve replacement, whilst the other 45 (43%) mitral valve repair. Patients who underwent surgical intervention also had CABG performed in 87 (82%) of cases, and 3 (3%) underwent combined procedures with other valvular interventions.

The time period between the index MI event and the mitral valve procedure was directly related to the type of intervention. Overall, although patients treated with PMVR were clinically worse, SMVR was performed earlier than PMVR [median of 12 days from MI date (IQR 5–19) vs. 19 days (10–40),  $P < 0.01$ ] (Table 2). Immediate procedural success was high in mitral interventions, reaching 92% of patients (98 of 106) in SMVR and 93% (92 of 99) in PMVR ( $P = 0.53$ ).

However, peri-procedural major complication rates were significantly higher in the surgical group (34% vs. 6%,  $P < 0.01$ ).

## Procedural outcomes

In both intervention groups, when compared with baseline, echocardiographic evaluation showed a marked reduction in MR at discharge (Figure 2A). Compared with baseline, NYHA functional class improved significantly at discharge (Figure 2B) in both intervention groups. Systolic PAP was significantly reduced after PMVR ( $54 \pm 20$  to  $43 \pm 20$  mmHg,  $P < 0.01$ ) and non-significantly reduced after SMVR ( $39 \pm 15$  to  $35 \pm 14$  mmHg,  $P = 0.14$ ) (Figure 2C).

## Mortality analysis—conservative vs. intervention

In-hospital mortality was highest among patients treated conservatively, reaching 27%, compared with 11% following mitral valve intervention ( $P < 0.01$ ). Survival curves for mortality are shown in Figure 3A and predictors for in-hospital mortality are reported in Table 3.



**Table 2** Procedural details and patient outcomes of surgical mitral valve repair or replacement and percutaneous mitral valve repair

| Variable                      | SMVR<br>(n = 106) | PMVR<br>(n = 99) | P-value         |
|-------------------------------|-------------------|------------------|-----------------|
| Procedure                     |                   |                  |                 |
| Procedure time, min           | 150 [118–240]     | 90 [60–136]      | <b>&lt;0.01</b> |
| MI to Procedure, days         | 12 [5–19]         | 19 [10–40]       | <b>&lt;0.01</b> |
| MR >2 at discharge            | 9 (8)             | 8 (8)            | 0.80            |
| Major complications           | 36 (34)           | 6 (6)            | <b>&lt;0.01</b> |
| Outcomes                      |                   |                  |                 |
| Procedure success             | 98 (92)           | 92 (93)          | 0.53            |
| In-hospital mortality         | 17 (16)           | 6 (6)            | <b>0.03</b>     |
| Mortality at 3 months         | 21 (20)           | 10 (10)          | 0.13            |
| Rehospitalization at 3 months | 6 (6)             | 13 (13)          | 0.14            |
| 1-year mortality              | 32 (31)           | 16 (17)          | <b>0.04</b>     |

Values are given as median [interquartile range], or n (%).  
MI, myocardial infarction; MR, mitral regurgitation; PMVR, percutaneous mitral valve repair; SMVR, surgical mitral valve repair or replacement.  
Values in bold are statistically significant p-values.

As shown in [Supplementary material online, Table S1](#), age, EUROSCORE II, anterior wall involvement, Killip class  $\geq 3$ , LVEF, cardiogenic shock, mechanical ventilation, use of mechanical circulatory support (MCS), and mitral intervention were all predictors of in-hospital mortality. Following adjustment for age, Killip class  $\geq 3$ , and use of MCS, conservative treatment was associated with an increased risk for in-hospital mortality (odds ratio 4.52, 95% CI 2.38–8.60,  $P < 0.01$ ).

In Cox regression analysis, following adjustment for age, Killip class  $\geq 3$ , LVEF, and use of MCS, conservative treatment was associated with increased risk for mortality at 1-year follow-up (crude HR 2.14, 95% CI 1.51–3.02,  $P < 0.001$ ; adjusted HR 3.53, 95% CI 2.18–5.73,  $P < 0.01$ ).

### Mortality analysis—surgical mitral valve repair or replacement vs. percutaneous mitral valve repair

In-hospital mortality was significantly higher in patients following SMVR when compared with patients treated with PMVR (16% vs. 6%,  $P < 0.01$ ) ([Table 2](#)).

As shown in [Supplementary material online, Table S2](#), age, EUROSCORE II, cardiogenic shock, and use of vasoactive medication and type of intervention were all predictors of mortality.

The difference in mortality between groups was also consistent at 1-year follow-up (31% vs. 17%,  $P = 0.04$ ). Kaplan–Meier curves are shown in [Figure 3B](#). In Cox regression analysis, SMVR was associated with a higher risk of mortality compared with PMVR (crude HR 2.45, 95% CI 1.09–5.50,  $P = 0.03$ ; adjusted HR 3.75, 95% CI 1.55–9.07,  $P < 0.01$ ).

When patients who died in-hospital were excluded from the analysis, there was no significant difference in 1-year mortality between SMVR and PMVR (log-rank,  $P = 0.44$ ) ([Figure 3C](#)).

The median EUROSCORE II of patients who underwent mitral intervention was 10% (IQR 5–19). The mortality rates according to EUROSCORE II are presented in [Figure 4](#). The survival benefit of PMVR over SMVR was observed in the low EUROSCORE II group ( $P = 0.04$ ) and in the high EUROSCORE II groups ( $P = 0.07$ ). Patients with EUROSCORE II above than 10% in the SMVR group had the worst outcomes with extremely high in-hospital mortality reaching 23% and 1-year mortality reaching 38%.

### Propensity score matching

Matching on estimated propensity score made available a matched cohort of 113 patients for each of the intervention and conservative groups, and 38 for each of the PMVR and SMVR groups with similar demographic, clinical, and angiographic clinical profiles ([Supplementary material online, Tables S3 and S4](#)). The in-hospital mortality was higher in the conservative group (35% vs. 12%,  $P < 0.01$ ) and conservative treatment was associated with increased mortality risk (HR 2.63, 95% CI 1.48–4.67,  $P < 0.01$ ).

In propensity-matched patients, in the PMVR group, the rate of in-hospital mortality was lower compared with the SMVR group (0% vs. 18%,  $P = 0.04$ ).

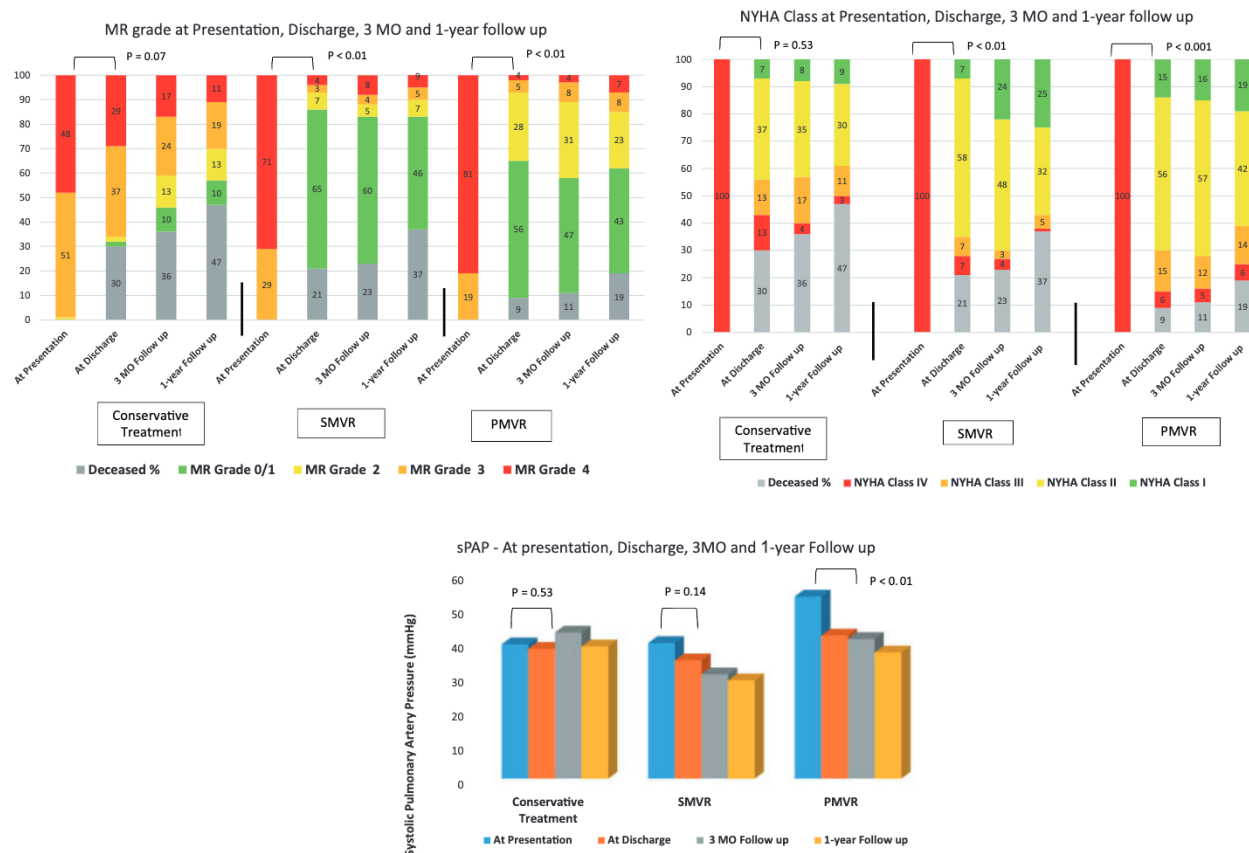
### Discussion

This current analysis is the largest and most comprehensive evaluation of different therapeutic strategies in patients with acute MI complicated by severe MR. To the best of our knowledge, this is the first and only analysis that compares outcomes of PMVR with other clinical strategies in this acute and complex setting. Patients who were treated conservatively had the worst prognosis. Mitral valve interventions, both percutaneous and surgical, had high success rates and were associated with better survival outcomes than conservative therapy. Nevertheless, patients who underwent SMVR had high peri-operative mortality, and more than 15% died during hospitalization. Our findings suggest that PMVR can serve as an alternative for surgery in reducing MR for high-risk patients with significant post-MI MR ([Graphical abstract](#)).

### Pathogenesis and epidemiology of post-myocardial infarction mitral regurgitation

Ischaemic MR complicating acute MI can be caused by a mechanical complication of papillary muscle rupture or by secondary mechanism due to global or regional LV remodelling.<sup>14</sup> The prevalence of this condition varies between different studies and peaks at 50% of all MI patients in some case series, while more than 10% of all ST-elevation MI patients develop significant MR (defined as moderate to severe or severe).<sup>15</sup> Mitral regurgitation causes volume overload and increased ventricular wall stress, causing further LV dilatation and worsening MR.<sup>14</sup> Mitral regurgitation on presentation or persistent ischaemic MR is known to be a negative prognostic factor, associated with poor short- and long-term prognosis.<sup>16</sup>

In our cohort, in-hospital and 1-year mortality rates were 20% and 36%, respectively, among patients with severe MR who were conservatively treated. These mortality rates are consistent with current literature. The mortality of MI patients according to

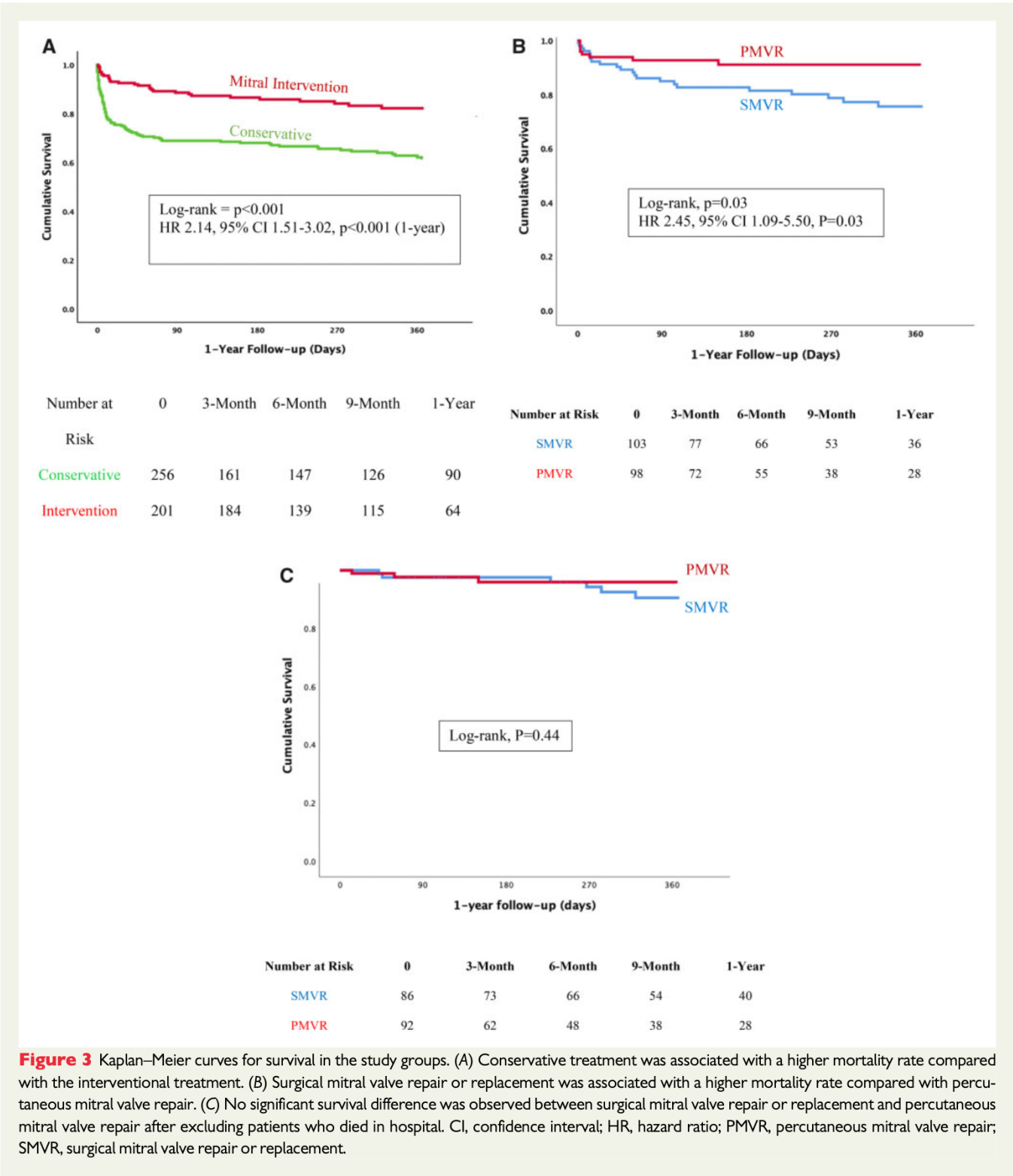


**Figure 2** Clinical and echocardiographic evaluation in the study groups at presentation, discharge, 3-month (MO) follow-up and 1-year follow-up. (A) Mitral regurgitation (MR) was significantly reduced from presentation to discharge in the intervention groups (surgical mitral valve repair or replacement and percutaneous mitral valve repair) but not in the conservative group. (B) New York Heart Association (NYHA) class was significantly improved from presentation to discharge in the intervention groups (surgical mitral valve repair or replacement and percutaneous mitral valve repair) but not in the conservative group. (C) Systolic pulmonary artery pressure (sPAP) was significantly reduced from presentation to discharge in percutaneously treated patients. PMVR, percutaneous mitral valve repair; SMVR, surgical mitral valve repair or replacement.

MR level was described by Tchong *et al.*<sup>6</sup> The 30-day mortality rates of patients with moderate-to-severe MR and severe MR were 19.8% and 26.1%, respectively, and at 1 year almost 40% in both groups died. While several studies pointed to the fact that post-MI MR is an independent risk factor for reduced long-term survival, the management of this condition is undetermined, and no studies have compared medical therapy to SMVR or any other intervention early after MI.<sup>17</sup> Furthermore, the effects of MR correction combined with CABG are not yet defined and the choice of the mitral valve procedure is still debated. The Randomized Ischaemic Mitral Evaluation (RIME) trial showed that adding mitral annuloplasty to CABG in patients with ischaemic MR improved functional capacity and promoted reverse remodelling.<sup>18</sup> However, large-scale trials and meta-analysis suggested that the addition of mitral valve repair to CABG did not result in reverse remodelling or clinical benefits.<sup>19,20</sup> In all of these studies, SMVR was performed in relatively stable patients and not in an acute setting.

## Management of post-myocardial infarction acute mitral regurgitation

Besides surgical intervention, current guidelines recommend intravenous diuretic, vasodilator, inotropic support, or MCS in order to stabilize patients with post-MI acute MR.<sup>7</sup> However, SMVR in an acute setting is often high risk. Our data suggest that short-term mortality after SMVR is high. These findings also correlate with previous observations. Lorusso *et al.*<sup>21</sup> evaluated the outcomes of 279 patients who underwent emergency surgery for acute severe MR and found that the overall 30-day mortality was 22.5% and that recent MI was a predictor for mortality. In the SHOCK (SHould We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock?) trial registry, most patients with post-MI cardiogenic shock and severe MR were treated conservatively. Patients treated medically were often deemed too sick to be operated on and had an in-hospital mortality rate of 55%. Among patients who underwent SMVR, the in-hospital mortality rate was 39%.<sup>22</sup> Similar findings were reported by Chevalier *et al.*<sup>23</sup>



Surgical mitral valve repair or replacement vs. percutaneous mitral valve repair

The high surgical mortality in this population could be attributed to patients' haemodynamic instability, complications of cardiopulmonary bypass, recent MI, and potent antiplatelet therapy. Importantly,

our findings suggest that patients who survive the acute phase and the early postoperative period have relatively good long-term outcomes. In fact, after excluding in-hospital mortality, the survival rates of PMVR and SMVR were similar. The in-hospital survival benefit of PMVR suggests that it can serve as a salvage therapy for patients that are at high risk for surgery allowing recovery in an acute setting.



**Table 3** Univariable and multivariable model, 1 year

| Variable               | Univariate       |                 | Multivariate          |                 |
|------------------------|------------------|-----------------|-----------------------|-----------------|
|                        | HR (95% CI)      | P-value         | HR (95% CI)           | P-value         |
| Age                    | 1.04 (1.03–1.06) | <b>&lt;0.01</b> | 1.05 (1.02–1.07)      | <b>&lt;0.01</b> |
| Sex                    | 1.18 (0.83–1.69) | 0.35            |                       |                 |
| Hypertension           | 1.62 (1.05–2.50) | <b>0.03</b>     | 1.09 (0.69–1.73)      | 0.70            |
| Diabetes mellitus      | 1.52 (1.07–2.17) | <b>0.02</b>     | 1.33 (0.91–1.96)      | 0.15            |
| Dyslipidaemia          | 0.94 (0.66–1.34) | 0.94            |                       |                 |
| Prior stroke           | 1.01 (0.51–1.99) | 0.97            |                       |                 |
| Prior MI               | 1.26 (0.82–1.91) | 0.29            |                       |                 |
| CKD >2                 | 1.63 (1.13–2.35) | <b>0.01</b>     | 1.03 (0.68–1.57)      | 0.88            |
| EuroSCORE II           | 1.04 (1.03–1.05) | <b>&lt;0.01</b> | 1.05 (1.03–1.05)      | <b>&lt;0.01</b> |
| STEMI presentation     | 1.08 (0.60–1.96) | 0.80            |                       |                 |
| Involved wall—anterior | 1.58 (1.09–2.30) | 0.06            | 1.03 (0.69–1.53)      | 0.90            |
| Killip class $\geq 3$  | 2.24 (1.54–3.25) | <b>&lt;0.01</b> | 2.31 (1.42–3.74)      | <b>&lt;0.01</b> |
| Multivessel CAD        | 1.17 (0.80–1.71) | 0.41            |                       |                 |
| PCI                    | 0.75 (0.51–1.11) | 0.15            |                       |                 |
| LVEF                   | 0.97 (0.96–0.99) | <b>&lt;0.01</b> | 0.974 (0.98–1.01)     | 0.71            |
| Mechanical ventilation | 2.27 (1.56–3.31) | <b>&lt;0.01</b> | Represented in Killip |                 |
| Cardiogenic shock      | 3.04 (2.13–4.35) | <b>&lt;0.01</b> | Represented in Killip |                 |
| Any MCS                | 1.38 (0.93–2.04) | 0.11            | 2.12 (1.28–3.50)      | <b>&lt;0.01</b> |
| Any intervention       | 0.37 (0.25–0.56) | <b>&lt;0.01</b> | 0.26 (0.17–0.45)      | <b>&lt;0.01</b> |

CAD, coronary artery disease; CKD, chronic kidney disease; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; PMVR, percutaneous mitral valve repair; SMVR, surgical mitral valve repair or replacement; STEMI, ST-elevation myocardial infarction.

Values in bold are statistically significant p-values.

When compared with SMVR, patients who underwent PMVR were older, had more comorbidities and prior cardiac conditions. For example, 27% of patients who underwent PMVR had a prior history for CABG compared with <1% in the surgical group. In addition, 67% of patients who underwent PMVR presented with Killip class  $\geq 3$ , 39% required mechanical ventilation and all patients remained symptomatic despite optimal medical therapy.

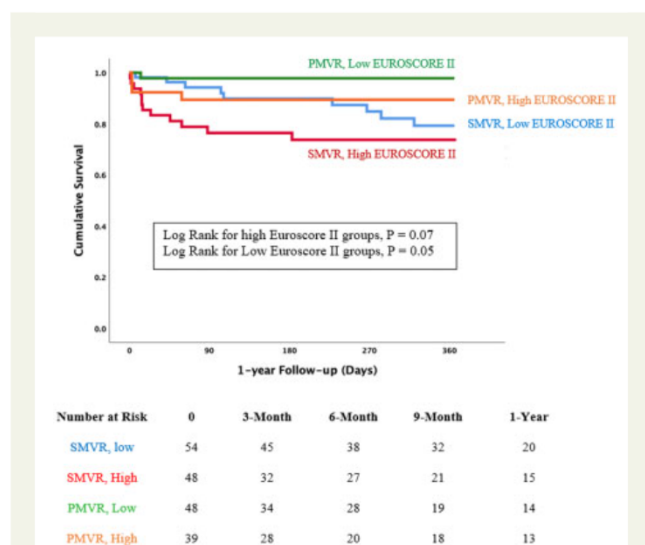
Although patients treated with PMVR had more comorbidities and more of them were in cardiogenic shock, the timing between index MI and PMVR was delayed when compared with patients who had SMVR. This finding may be attributed to several factors. First, PMVR in an acute setting is still not common practice, and the availability for this therapy, especially in an emergency context, is limited when compared with surgical intervention. Therefore, in many cases, PMVR was performed late in the course of the disease and only after other mechanical and medical therapy failed; it was also offered to patients that were excluded from surgery. Second, although patients in the PMVR group had higher risk scores, it is possible that other clinical unmeasured confounders led to earlier intervention in the surgical intervention.

Patients with a high EUROSCORE II who underwent surgery had high in-hospital mortality of almost 25% and therefore might be considered for PMVR strategy. Our findings may imply that intervention should not be delayed, especially considering the high safety profile of this approach and that PMVR does not preclude a future surgical intervention in case of device failure.

## Limitations

Several potential limitations of this study merit consideration. First, all participating centres were requested to include all the patients who were eligible according to the inclusion criteria. Although the case number is high, the included procedures are spread over 21 centres, a long period of time and by the nature of this multicentre retrospective analysis, it is possible that not all patients were enrolled. Second, despite multivariable adjustment and matching, the associations between baseline characteristics and outcomes may be confounded by unmeasured variables. In addition, patient allocation to each therapy may be biased due to clinical factors that affected physician decision-making. Third, laboratory data, medications, detailed and Corelab echocardiographic evaluation is lacking, and therefore, the effect on LV remodelling has not been evaluated. However, the study was designed for evaluating the impact of intervention on survival in high-risk populations as a proof-of-concept study. Fourth, PMVR procedures were performed at highly experienced centres and it should be acknowledged that PMVR early after MI might be technically challenging due to valve complexity, a small left atrium, and the clinical condition of patients. Fifth, in all our cases, PMVR was performed as a salvage procedure in critically ill patients. Therefore, the findings cannot be generalized for mildly symptomatic patients who develop ischaemic MR after MI.

Finally, our analysis should be considered hypothesis generating. Therefore, randomized trials are required to validate our findings and determine the optimal treatment for post-MI acute MR.



**Figure 4** Kaplan–Meier curve comparing 1-year survival of surgical mitral valve repair or replacement and percutaneous mitral valve repair according to the median EUROSCORE II. The survival benefit of percutaneous mitral valve repair over surgical mitral valve repair or replacement was observed in the low EUROSCORE II group ( $P=0.04$ ) and in the high EUROSCORE II groups ( $P=0.07$ ). EUROSCORE II, European System for Cardiac Operative Risk Evaluation; PMVR, percutaneous mitral valve repair; SMVR, surgical mitral valve repair or replacement

## Conclusions

Post-MI severe MR is associated with poor outcomes. Patients were often in extreme clinical condition but interventions, both surgical and percutaneous, resulted in favourable outcomes. Percutaneous mitral valve repair was successful in decreasing MR and improved haemodynamic parameters and should be considered as an alternative for patients that are deemed high risk for surgical intervention.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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## 10.5. Anexo 5

Use of MitraClip for mitral valve repair in patients with acute mitral regurgitation following acute myocardial infarction: effect of cardiogenic shock on outcomes. IREMMI registry (International Registry of MitraClip in acute Myocardial Infarction).

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## ORIGINAL STUDIES

WILEY

EDITORIAL COMMENT: Expert Article Analysis for:

Tailwind of transcatheter mitral valve repair pushes forward the treatment of acute mitral regurgitation after myocardial infarction

# Use of MitraClip for mitral valve repair in patients with acute mitral regurgitation following acute myocardial infarction: Effect of cardiogenic shock on outcomes (IREMMI Registry)

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**Abbreviations:** AMI, acute myocardial infarction; CS, cardiogenic shock; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MVARC, Mitral Valve Academic Research Consortium; NYHA, New York Heart Association; PMVR, percutaneous mitral valve repair; SPAP, systolic pulmonary arterial pressure.

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**Abstract**

**Objectives:** To assess outcomes in patients with acute mitral regurgitation (MR) following acute myocardial infarction (AMI) who received percutaneous mitral valve repair (PMVR) with the MitraClip device and to compare outcomes of patients who developed cardiogenic shock (CS) to those who did not (non-CS).

**Background:** Acute MR after AMI may lead to CS and is associated with high mortality.

**Methods:** This registry analyzed patients with MR after AMI who were treated with MitraClip at 18 centers within eight countries between January 2016 and February 2020. Patients were stratified into CS and non-CS groups. Primary outcomes were mortality and rehospitalization due to heart failure. Secondary outcomes were acute procedural success, functional improvement, and MR reduction. Multivariable Cox regression analysis evaluated association of CS with clinical outcomes.

**Results:** Among 93 patients analyzed (age  $70.3 \pm 10.2$  years), 50 patients (53.8%) experienced CS before PMVR. Mortality at 30 days (10% CS vs. 2.3% non-CS;  $p = .212$ ) did not differ between groups. After median follow-up of 7 months (IQR 2.5–17 months), the combined event mortality/re-hospitalization was similar (28% CS vs. 25.6% non-CS;  $p = .793$ ). Likewise, immediate procedural success (90% CS vs. 93% non-CS;  $p = .793$ ) and need for reintervention (CS 6% vs. non-CS 2.3%,  $p = .621$ ) or re-admission due to HF (CS 13% vs. NCS 23%,  $p = .253$ ) at 3 months did not differ. CS was not independently associated with the combined end-point (hazard ratio 1.1; 95% CI, 0.3–4.6;  $p = .889$ ).

**Conclusions:** Patients found to have significant MR during their index hospitalization for AMI had similar clinical outcomes with PMVR whether they presented in or out of cardiogenic shock, provided initial hemodynamic stabilization was first achieved before PMVR.

**KEYWORDS**

acute myocardial infarction, cardiogenic shock, MitraClip, mitral regurgitation, percutaneous mitral valve repair

## 1 | INTRODUCTION

Acute mitral regurgitation (MR) may develop in the setting of an acute myocardial infarction (AMI) as a result of papillary muscle dysfunction or rupture. Acute MR is a severe complication that may occur in up to 3% of AMI patients, is more prevalent in patients presenting with hemodynamic instability, and has been linked to a worse prognosis even in the modern era of transcatheter reperfusion.<sup>1–4</sup> Acute MR without papillary muscular rupture may induce severe MR due to leaflet tethering produced by the sudden onset of regional or global left ventricular dysfunction and can lead to pulmonary edema or cardiogenic shock (CS) during the acute or subacute phase of the MI.<sup>5</sup> Thus, more commonly patients who present with AMI may also be found to have severe functional mitral regurgitation. Although percutaneous revascularization may improve the degree of MR,<sup>4</sup> in some cases, MR remains unaltered or worsens,

potentially leading to clinical deterioration that may prompt intervention.

Until recently, the only intervention for correcting MR was surgery; however, surgery is associated with high rates of morbidity and increased mortality nearing 20–25%.<sup>6</sup> Additionally, patients treated solely with medical therapy have the highest mortality rates.<sup>7</sup> Therefore, the development of less invasive interventions for repairing MR would be beneficial. The method of percutaneous mitral valve repair (PMVR) with the MitraClip device (Abbot Vascular, Santa Clara, California) has been shown to be a safe and effective technique for reducing MR in patients who are at high risk for open-heart surgery,<sup>8</sup> and this method can improve symptoms, quality of life, and prognosis in patients with functional MR.<sup>9–12</sup> Whereas most MR cases are in patients who are in a stable clinical situation with advanced functional class and chronic MR, patients with acute MR are underrepresented in registries and randomized trials.

Although experiences with MitraClip for correcting MR following AMI have been reported,<sup>13-17</sup> data on the effect of this treatment in patients who develop CS during the event are lacking, and the issue remains understudied. The aim of this registry-based study was to assess procedural, clinical, and echocardiographic outcomes of patients with acute MR after AMI who were treated by PMVR with the MitraClip device and to assess whether patients who developed CS had different outcomes from those who did not (non-CS).

## 2 | METHODS

We performed a registry-based record review study by assessing all consecutive patients who were found to have severe MR when presenting with AMI and who underwent PMVR with the MitraClip device in 18 centers worldwide between January 2016 and January 2020. A list of participating centers is shown in Table S1.

## 3 | PATIENT POPULATION

### 3.1 | Inclusion criteria

Patients were included in the study who had an AMI in the prior 4 weeks and experienced symptomatic severe MR that was diagnosed by transthoracic echocardiogram or transesophageal echocardiogram following current guidelines and recommendations.<sup>18,19</sup> Symptoms of MR were different from heart failure to CS. All patients were considered by a heart team to be at high risk for conventional surgery.

### 3.2 | Exclusion criteria

Patients were excluded if their anatomy was not suitable for MitraClip implantation.

All patients were cared for following current practice guidelines for both AMI and acute heart failure.<sup>6,20</sup> Administration of intravenous diuretics and inotropes/vasopressors and indication for mechanical ventilation or circulatory support before PMVR were conducted based on attending team criteria. Patients with CS included those patients who fulfilled the CS definition of the Society for Cardiovascular Angiography and Intervention Stage C-E.<sup>21</sup> The timing of shock evaluation to classify patients was the time of MitraClip strategy decision.

### 3.3 | Procedure

All procedures were performed in a cardiac catheterization laboratory or in a hybrid room, and patients were under general anesthesia using transesophageal echocardiogram and fluoroscopic guidance. Preprocedural transthoracic and transesophageal echocardiography were

performed in all patients for semiquantitative MR analysis and to assess morphologic suitability for MitraClip implantation.

### 3.4 | Study end points

Baseline and echocardiographic features and immediate procedural outcomes were collected. Procedural and clinical adverse events during follow-up were defined according to the Mitral Valve Academic Research Consortium.<sup>22</sup> Technical success was defined as correct implantation of at least one clip and the absence of procedural mortality or emergent cardiovascular intervention related to the device or the access site. Immediate procedural success was defined as technical success associated with a reduction of MR to  $\leq 2+$ . Procedural success at 30-days follow-up was defined as device success in the absence of life-threatening bleeding, major vascular or structural complications, MI, severe acute kidney injury, or hemodynamic instability. Total mortality and admission due to heart failure were the main clinical end-points. Secondary outcomes were acute procedural success, periprocedural complications, functional improvement, and MR reduction.

Echocardiographic and clinical follow-up were carried out per New York Heart Association functional classification. Patients were contacted by phone if necessary. Data collection was approved by the local ethics committee of every institution and written informed consent was obtained.

### 3.5 | Statistical analysis

Continuous variables were summarized as mean  $\pm$  SD or as median and interquartile range (IQR). Comparisons were made using unpaired Student's *t*-test or the nonparametric Wilcoxon rank sum test if data did not follow a normal distribution. Distribution normality was assessed with the Shapiro-Wilk test. Categorical variables were described as percentages and were compared using Chi-square test for frequencies greater than 5 and Fisher exact test for frequencies less than 5. Survival curves for time-to-event were constructed using all available follow-up data with Kaplan-Meier estimates. Comparisons between CS and non-CS patients were performed using the log-rank test. A Cox-regression analysis adjusted by age, EuroScore II, and acute procedural success was performed to evaluate the independent effect of CS on clinical events. A *p*-value  $< .05$  was considered statistically significant. Statistical analyses were performed using SPSS version 25.0. (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

## 4 | RESULTS

A total of 93 records in the IREMMI registry of patients who had mitral valve repair with the MitraClip device between January 2016 and February 2020 were included in the study. The mean  $\pm$  SD

**TABLE 1** Baseline characteristics

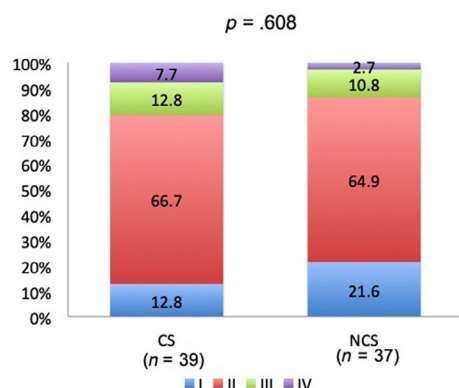
|                                   | Total <i>n</i> = 93 | CS <i>n</i> = 50 | Non-CS <i>n</i> = 43 | <i>p</i> -value |
|-----------------------------------|---------------------|------------------|----------------------|-----------------|
| Variables                         |                     |                  |                      |                 |
| Age, years                        | 70 ± 10             | 68 ± 10          | 72 ± 9               | .061            |
| Male, <i>n</i> (%)                | 45 (48)             | 25 (50)          | 20 (46)              | .836            |
| Diabetes, <i>n</i> (%)            | 40 (43)             | 23 (46)          | 17 (40)              | .672            |
| Hypertension, <i>n</i> (%)        | 65 (70)             | 33 (66)          | 32 (74)              | .486            |
| BMI (kg/m <sup>2</sup> )          | 26 ± 5              | 26 ± 4           | 26 ± 5               | .574            |
| Dyslipidaemia, <i>n</i> (%)       | 58 (62)             | 28 (56)          | 30 (69)              | .192            |
| COPD, <i>n</i> (%)                | 16 (17)             | 7 (14)           | 9 (21)               | .417            |
| Previous MI, <i>n</i> (%)         | 53 (57)             | 28 (56)          | 25 (58)              | 1.000           |
| Previous stroke, <i>n</i> (%)     | 13 (14)             | 9 (18)           | 4 (9)                | .368            |
| Previous CABG, <i>n</i> (%)       | 25 (27)             | 14 (28)          | 11 (25)              | .817            |
| Previous CKD, <i>n</i> (%)        | 45 (48)             | 20 (40)          | 25 (58)              | .081            |
| Euroscore 2, mean ± SD            | 16 ± 15             | 21 ± 18          | 11 ± 8               | .001            |
| Infarct location                  |                     |                  |                      | .013            |
| Anterior                          | 32 (35)             | 23 (46)          | 9 (21)               |                 |
| Inferior                          | 44 (47)             | 16 (32)          | 28 (65)              |                 |
| Lateral                           | 15 (16)             | 10 (20)          | 5 (12)               |                 |
| Undetermined                      | 2 (2)               | 1 (2)            | 1 (2)                |                 |
| STEMI, <i>n</i> (%)               | 68 (73.1)           | 39 (78)          | 29 (67.4)            | .502            |
| Multivessel disease, <i>n</i> (%) | 73 (78)             | 38 (76)          | 36 (83)              | .404            |
| Primary PCI, <i>n</i> (%)         | 66 (71)             | 38 (76)          | 28 (65)              | .159            |
| MCS                               |                     |                  |                      |                 |
| IABP/Impella                      | 36 (38)             | 33 (66)          | 3 (7)                | <.001           |
| VA ECMO                           | 6 (6)               | 6 (12)           | 0 (0)                | .028            |
| Vasoactive drugs                  | 43 (46)             | 41 (82)          | 2 (4)                | <.001           |
| LVEF (%)                          | 36 ± 12             | 34 ± 12          | 38 ± 11              | .079            |
| MR grade 4+, <i>n</i> (%)         | 77 (83)             | 43 (86)          | 34 (79)              | .377            |
| Systolic PAP (mmHg)               | 54 ± 19             | 53 ± 21          | 55 ± 18              | .793            |

Abbreviations: BMI, body mass index; CABG, coronary artery by-pass graft; CKD, chronic kidney disease; COPD, Chronic obstructive pulmonary disease; CS, cardiogenic shock; IABP, intraaortic balloon pump; LVEF, left ventricle ejection fraction; MCS, mechanical cardiac support; MI, myocardial infarction; MR, mitral regurgitation; NCS, non-cardiogenic shock; PCI, percutaneous coronary intervention; PAP, pulmonary artery pressure; STEMI, ST-segment elevation myocardial infarction; VA ECMO, veno-arterial extracorporeal membrane oxygenation.

patient age was 70.3 ± 10.2 years and included 48 (51.6%) women and 45 (48.4%) men. Characteristics of the population are in Table 1. Patients were divided into CS and non-CS groups. Of the 93 patients, 50 (53.8%) were in CS prior to MitraClip procedure. SCAI categories of cardiogenic shock were A 24.7%, B 21.5%, C 36.6%, D 15.1%, and D 2.1%. Compared with non-CS patients, patients with CS were younger (68 ± 10 vs. 72 ± 9 years; *p* = .061), had a lower prevalence of chronic kidney disease (40 vs. 58%; *p* = .081), had higher surgical risk (21 ± 18% vs. 11 ± 8% Euroscore II; *p* = .001), and had shorter time elapsed between MI and MitraClip placement (24 ± 22 vs. 33 ± 23 days; *p* = .069) (Table 1). The prevalence of multi-vessel disease was high (CS, 76% vs. non-CS, 83%; *p* = .404) and similar between groups and anterior wall MI was more frequent in the CS group (CS, 46% vs. non-CS, 21%;

*p* = .013). The percentage of primary percutaneous coronary intervention was equivalent. Complete revascularization was achieved in 86% of patients with multivessel disease, with no difference between CS and non-CS patients (*p* = .562). CS patients were prescribed vasoactive drugs more frequently (82 vs. 4%, *p* < .001) and were more likely to have IABP/Impella pumps (66 vs. 7%, *p* < .001) or venoarterial extra-corporeal membrane oxygenation (12 vs. 0%, *p* = .028). Of the patients with IABP, 3 non-CS patients received prophylactic IABP implantation after diagnosis with severe MR. Preprocedural MR was 4+ in 86% of CS patients and 79% in non-CS patients (*p* = .377). Left ventricular ejection fraction was lower in CS patients, but no differences were observed regarding systolic pulmonary arterial pressure (SPAP). Six patients were reported to have partial or complete papillary muscle rupture.





**FIGURE 1** New York Heart Association functional class at 3 months [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

#### 4.1 | Procedural characteristics

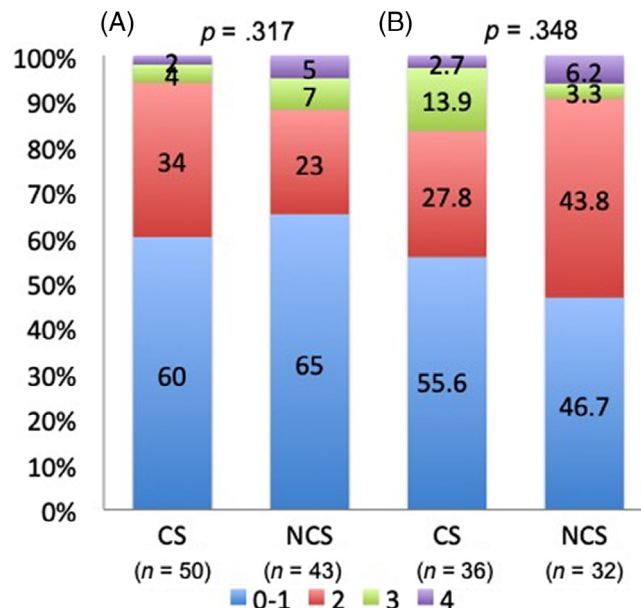
Technical success was achieved in 100% of patients. MitraClip NT and NTR devices were used in 80 patients, XTR devices were used in 10 patients, and a combination of clips was used in 3 patients. More than 1 clip was used in 58.1% of patients. Immediate procedural success was high, with no difference between groups (CS, 90% vs. non-CS, 93%,  $p = .793$ ). However, mean procedure length was longer in patients with CS than in non-CS patients ( $143 \pm 113$  vs.  $82 \pm 44$  min;  $p = .003$ ).

The percentage of in-hospital major complications (including partial clip detachment, air embolism, MI, stroke, vascular injury, pericardial effusion, and bleeding events) was low after procedure and did not differ between groups (CS, 4% vs. non-CS, 7%,  $p = .659$ ). Overall, mean SPAP was significantly decreased after the procedure (before,  $54 \pm 19$  mmHg vs. after,  $44 \pm 20$  mmHg;  $p < .001$ ), with no difference between groups. The mean mitral valve gradient increased significantly after procedure (before,  $1.7 \pm 0.9$  mmHg vs. after,  $3.3 \pm 1.6$  mmHg;  $p < .001$ ). After PMVR, the gradient did not differ between CS and non-CS patients (CS,  $3.7 \pm 1.9$  mmHg vs. non-CS,  $3.6 \pm 1.7$  mmHg;  $p = .741$ ).

#### 4.2 | Clinical follow-up

At 30-day follow-up, mortality was higher in the CS group (10 vs. 2.3%), but the difference was not significant ( $p = .207$ ). Procedural success at 30 days was lower in patients with CS, but the difference was not significant (CS, 59% vs. non-CS, 74%;  $p = .136$ ).

At 3-month follow-up, there were no differences in the percentage of re-admissions due to heart failure (CS, 13% vs. non-CS, 23%,  $p = .253$ ) or repeated MitraClip intervention or surgery (CS, 6% vs. non-CS, 2.3%;  $p = .621$ ). New York Heart Association functional classifications improved significantly compared with baseline, but no differences were observed between groups (Figure 1). Likewise, echocardiographic evaluation during this period showed a marked reduction in MR with no difference between groups (Figure 2). Reduction in SPAP persisted, and no differences were observed between groups (CS,  $40 \pm 13$  mmHg vs. non-CS,  $44 \pm 19$  mmHg;  $p = .441$ ).



**FIGURE 2** MR reduction postprocedural (panel a) and at 3 months (panel b) [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

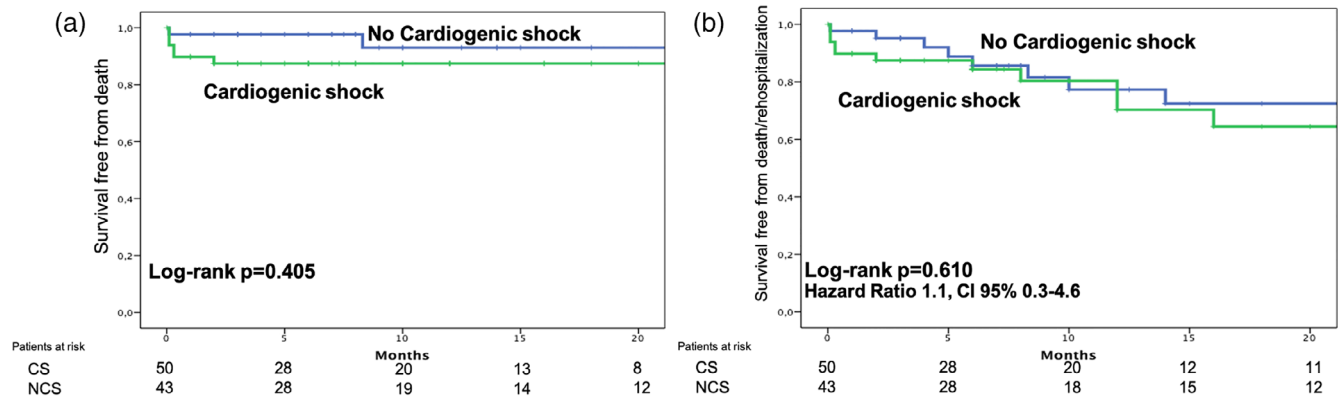
After a median follow-up of 7 months (range 0–81 months, IQR 2.7–17), overall mortality did not differ between groups (CS, 16% vs. NCS, 9.3%;  $p = .377$ ), and the combined event mortality/rehospitalization due to heart failure was similar (CS, 28% vs. NCS, 26%;  $p = .793$ ). Survival curves for both end-points are shown in Figure 3.

In a Cox-regression analysis adjusted by age, Euroscore II, and procedural success, CS was not independently associated with the combined end-point (hazard ratio [HR], 1.1; 95% CI, 0.3–4.6;  $p = .889$ ). The only variable independently associated with the combined end-point was the immediate procedural success (HR, 0.1; 95% CI, 0.01–0.6;  $p = .012$ ). Univariate and multivariate analyses are shown in Table 2.

## 5 | DISCUSSION

To our knowledge, this is the largest registry-based study evaluating the outcomes of patients who developed acute MR after AMI and who received PMVR with the MitraClip device. Our data suggest that this procedure may be a safe and effective strategy for reducing MR and improving prognosis in such high-risk populations. Also, we observed no differences in outcomes after PMVR in patients with CS, suggesting that CS may not be an important factor for precluding implementation of the therapy, providing that clinical stabilization could be achieved to receive PMVR.

MR after AMI is a serious complication that occurs in roughly 3% of cases. Complete papillary muscle rupture is uncommon (0.25% of MIs in the percutaneous coronary intervention era) and is often fatal.<sup>23</sup> However, acute MR due to leaflet tethering, partial papillary muscle



**FIGURE 3** Kaplan-Meier survival curves comparing CS and non-CS groups. Panel a: Survival free from death. Panel b: Survival free from death and rehospitalization due to heart failure [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

|                    | Univariate |           |          | Multivariate |           |          |
|--------------------|------------|-----------|----------|--------------|-----------|----------|
|                    | HR         | 95% CI    | <i>p</i> | HR           | 95% CI    | <i>p</i> |
| Age                | 0.99       | 0.95–1.03 | .651     | 1.05         | 0.97–1.13 | .227     |
| CKD                | 1.11       | 0.48–2.60 | .810     |              |           |          |
| DM                 | 1.90       | 0.81–4.46 | .140     |              |           |          |
| EuroScore II       | 1.02       | 0.99–1.05 | .087     | 1.02         | 0.99–1.06 | .154     |
| Pre IHD            | 0.98       | 0.38–2.56 | .979     |              |           |          |
| LVEF               | 0.99       | 0.95–1.03 | .592     |              |           |          |
| Cardiogenic shock  | 0.97       | 0.42–2.24 | .936     | 1.1          | 0.3–4.6   | .889     |
| Procedural success | 0.18       | 0.06–0.57 | .004     | 0.10         | 0.02–0.60 | .012     |
| MCS                | 0.60       | 0.23–1.54 | .288     |              |           |          |

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; DM, Diabetes Mellitus; HR, hazard ratio; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MCS, mechanical cardiac support.

**TABLE 2** Univariate and multivariate predictors of combined death/rehospitalization due to heart failure during follow-up

rupture, or new onset of left ventricular dysfunction may be more frequent, with a possible prevalence of 35%, according to a study of a series of MI treated by primary percutaneous coronary intervention.<sup>4</sup> In a cohort of surgical patients, complete papillary muscle rupture after MI-related MR was responsible for 45% of cases,<sup>24</sup> which means that severe functional MR after MI is common and may cause deterioration in a patient's condition enough to justify intervention.

Regarding treatment of MR (excluding complete papillary muscle rupture), it has been reported that revascularization by means of primary percutaneous coronary intervention can significantly improve the degree of MR and therefore should be a first line treatment.<sup>4</sup> In our study, primary percutaneous coronary intervention was carried out in almost 72% of cases. However, even after successful percutaneous revascularization, the degree of MR may worsen, and further treatment may be required. When CS develops within the context of MR, mortality rises significantly, and stabilization through pharmacological afterload reduction and/or mechanical circulatory support may be lifesaving. However, the use of this advanced support should not be a destination therapy, but rather a bridge to a subsequent interventional therapy focused in correcting MR.<sup>1,6,25</sup>

Until recently, cardiac surgery was the only option available for the treatment of MR, and a systematic review revealed a pooled 30-day mortality rate of 19%, with some studies showing mortality rates as high as 39%.<sup>7</sup> Notwithstanding, in recent years PMVR has been extensively developed, and MitraClip is the device that has been used for PMVR most extensively so far.

MitraClip has been shown to be safer than conventional surgery, although less effective.<sup>26</sup> In real-world registries of patients with both degenerative and functional MR and who are at high-risk for surgery, MitraClip use is associated with clinical improvements and a significant reduction of MR.<sup>10,11,27</sup> However, most MitraClip interventions performed to date have been in patients who were in a stable clinical situation with advanced functional class and chronic (not acute) MR. Our data suggest that MitraClip could be a safe and effective alternative to surgical intervention in clinically unstable patients who have a high risk of 30-day mortality, and this therapy may even be safe for the 10% of patients who develop CS, which is encouraging.

In our study, we saw that clinical results of PMVR did not differ significantly between CS and non-CS patients, despite the poorer

clinical situation and lower left ventricular ejection fraction in patients with CS. This underscores the fact that in a CS scenario, the main component responsible for clinical deterioration is the MR and its deleterious hemodynamic effects rather than the role of pump failure. This could explain the difference in mortality observed in our series compared with classic series of CS following MI<sup>28</sup> or in those series of PMVR in cardiogenic shock patients where patients were in a clinical unstable condition but after mainly a long-standing ischemic or non-ischemic cardiomyopathy in an end-stage situation.<sup>29-31</sup> On the other hand, the time from MI to MR treatment was several weeks in our patient sample, and this could be related to the intention to stabilize the clinical condition with the belief medical therapy was the only option for the MR, since patients were not surgical candidates and the MitraClip approach was rather new in this setting. However, treating the MR quickly produces such positive clinical benefits that the intervention should not be delayed. Thus, we advocate for early MR correction irrespective of lower left ventricular ejection fraction and development of CS.

There are several potential advantages of using PMVR with MitraClip. First, this treatment can lead to a rapid decrease in left ventricular, left atrium, and pulmonary artery pressures and an increase of cardiac output after a successful correction of the MR,<sup>32</sup> which may lead to a fast recovery. Second, the technique reduces risk of left ventricle damage induced by the systemic inflammatory response, free radical injury, and myocardial oxidative stress associated with cardiopulmonary bypass.<sup>33</sup> Moreover, MitraClip may also avoid the restraint of the mitral annular motion caused by mitral rings or prosthesis and the development of abnormal septal motion that may negatively impact left ventricle performance. In addition, acute MR often develops in a previously normal mitral valve, which usually translates into optimal leaflet tissue and coaptation for device therapy. Furthermore, the use of MitraClip does not preclude a delayed cardiac surgery in case the device fails. Finally, a relevant number of unstable patients are on double or triple antithrombotic therapy after MI, and MitraClip may help prevent significant bleeding complications that are common after open-heart surgery and that may negatively impact the prognosis of unstable patients. However, challenges when implementing this therapy exist. Treating acute MR is one of the most technically challenging MitraClip procedures. Lesion complexity, a small atrium that makes performing a high puncture difficult, the clinical situation of the patient, and the risk of impingement in papillary muscle make these cases very demanding. The fact that the only independent factor associated with clinical outcomes was immediate technical success underscores the relevance of the high level of experience required for the implanting team.

Interestingly, a recent review of shock management after MI<sup>25</sup> only considers mitral valve surgery for acute MR after MI. Our data suggest that, given the favorable safety/efficacy profile, PMVR should at least be considered in patients with this condition if the attending team has enough experience. This strategy may be of special interest in patients with CS, which represent complex cases where effective and fast recovery with a low rate of complications is desirable. Further

research and randomized trials are required to increase our knowledge in this setting.

## 6 | LIMITATIONS

Our study had several limitations. First, is an observational study and the sample size was small and so should be interpreted with caution. We did not find a significant difference in mortality between CS and non-CS patients, which could be related to a lack of statistical power. A larger study with longer follow-up will be needed to clarify the effect of MitraClip in this scenario. Furthermore, we cannot exclude the presence of a selection bias in CS patients, in the sense that only those who responded to the medical therapy and cardiac support were those who received PMVR. Time from MI to PMVR was long and that means that even CS patients responded to the medical therapy in some way. This population can represent a better prognostic category and therefore our conclusions may not be applicable to all patients in CS with significant MR. Likewise, because of the small sample size and number of events, the multivariable analysis was limited. Thus, results should be considered hypothesis generating and not generalizable. Also, echocardiographic follow-up is lacking, so the effect on left ventricular remodeling has not been evaluated. However, our aim was to assess correlation within the clinical setting, not to show possible positive effects on left ventricular parameters. Likewise, number of patients with subvalvular apparatus rupture was small to draw definitive conclusions. Although if a successful repair can be achieved results seemed similar, larger series with these anatomies must be collected to assess the specific performance of MitraClip in this population. The shock status is a dynamic variable and we defined it at the time of MitraClip strategy decision. What we cannot ascertain is what was the SCAI classification at the beginning of the clinical course. Likewise, all patients were treated with MitraClip as a salvage strategy, but we cannot distinguish from the present study whether the patients were stable enough or with recurrent deterioration despite MCS support. Lastly, procedures were performed in centers that had high levels of experience with PMVR using MitraClip. Thus, our findings cannot be generalized to less experienced teams.

## 7 | CONCLUSION

Patients found to have significant MR during their index hospitalization for AMI had similar clinical outcomes with PMVR whether they presented in or out of cardiogenic shock, provided initial hemodynamic stabilization was first achieved before PMVR.

### 7.1 | Clinical perspective

#### 7.1.1 | What is next?

Further research is warranted to confirm these results and to compare the percutaneous approach with conventional surgery.

### 7.1.2 | What is new?

PMVR with the MitraClip device may be a promising therapeutic strategy for patients with acute MR after AMI, with or without CS. This may represent a valid alternative for such patients.

### 7.1.3 | What is known?

Acute MR may develop following AMI, a condition associated with development of CS and high mortality. Until recently, conventional surgery was the only alternative, which is associated with significant mortality.

### CONFLICT OF INTEREST

Rodrigo Estévez-Loureiro is consultant for Abbott Vascular and Boston Scientific. Dr. Taramasso is a consultant for Abbott Vascular, Boston Scientific, 4TECH, and CoreMedic; and has received speaker honoraria from Edwards Lifesciences. Dr. Denti has served as a consultant for Abbott Vascular, 4Tech, Neovasc, and InnovaHeart; and has received honoraria from Abbott. Dabit Arzamendi is consultant for Abbott Vascular. Dr. Xavier Freixa is consultants for Abbott Vascular. Dr. Fam, has received speaker honoraria and travel or grant support from Edwards Lifesciences. Francesco Maisano received Grant and/or Research Support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific Corporation, NVT, Terumo; receives Consulting fees, Honoraria from Abbott, Medtronic, Edwards Lifesciences, Swissvortex, Perifect, Xeltis, Transseptal solutions, Cardiovalve, Magenta; has Royalty Income/IP Rights Edwards Lifesciences and is Shareholder of Cardiovalve, Cardiogard, Magenta, SwissVortex, Transseptalsolutions, 4Tech, Perifect. All other authors have reported that they have no relationships relevant to the contents of this article to disclose.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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## 10.6. Anexo 6

Safety and feasibility of MitraClip implantation in patients with acute mitral regurgitation after recent myocardial infarction and severe left ventricle dysfunction.

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Article

# Safety and Feasibility of MitraClip Implantation in Patients with Acute Mitral Regurgitation after Recent Myocardial Infarction and Severe Left Ventricle Dysfunction

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**Abstract:** Patients with severe mitral regurgitation (MR) after myocardial infarction (MI) have an increased risk of mortality. Transcatheter mitral valve repair may therefore be a suitable therapy. However, data on clinical outcomes of patients in an acute setting are scarce, especially those with reduced left ventricle (LV) dysfunction. We conducted a multinational, collaborative data analysis from 21 centers for patients who were, within 90 days of acute MI, treated with MitraClip due to severe MR. The cohort was divided according to median left ventricle ejection fraction (LVEF)—35%. Included in the study were 105 patients. The mean age was  $71 \pm 10$  years. Patients in the LVEF < 35% group were younger but with comparable Euroscore II, multivessel coronary artery disease, prior MI and coronary artery bypass graft surgery. Procedure time was comparable and acute success rate was high in both groups (94% vs. 90%,  $p = 0.728$ ). MR grade was significantly reduced in both groups along with an immediate reduction in left atrial V-wave, pulmonary artery pressure and improvement in New York Heart Association (NYHA) class. In-hospital and 1-year mortality rates were not significantly different between the two groups (11% vs. 7%,  $p = 0.51$  and 19% vs. 12%,  $p = 0.49$ ) and neither was the 3-month re-hospitalization rate. In conclusion, MitraClip intervention in patients with acute severe functional mitral regurgitation (FMR) due to a recent MI in an acute setting is safe and feasible. Even patients with severe LV dysfunction may benefit from transcatheter mitral valve intervention and should not be excluded.

**Keywords:** mitral regurgitation; percutaneous mitral valve repair; acute myocardial infarction; left ventricle dysfunction

## 1. Introduction

Mitral regurgitation (MR) complicating acute Myocardial Infarction (MI) can be the result of papillary muscle rupture (Primary) or imbalance between closing and tethering forces (Functional). Primary MR in this acute setting is a medical emergency often requires emergent intervention [1]. Functional mitral regurgitation (FMR) usually develops over the course of days and is associated with adverse outcomes [2]. Currently, medical therapy is the mainstay approach for this condition. However, some patients remain very symptomatic with prolonged hospitalization and frequent heart failure (HF) admissions [3].

Data obtained from large-scale registries suggest that percutaneous transcatheter edge-to-edge mitral valve repair implantation with MitraClip device improves functional capacity and quality of life [4–7]. Furthermore, the recent randomized trial entitled, ‘Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation’ (COAPT) showed that MitraClip improved clinical outcomes, including mortality in patients with severe FMR, when compared to medical therapy alone [8]. Conversely, the results of the ‘Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation’ (MITRA-FR) illustrated that enrolled patients with lower LVEF showed no clinical benefit from the MitraClip procedure in an advanced HF population [9], thereby suggesting that patients with lower LVEF may benefit less from the MitraClip procedure.

Focusing on patients with reduced left ventricle (LV) function, previous studies have addressed this issue with mixed results. In the German transcatheter mitral valve interventions (TRAMI) registry, the clinical benefit for patients with severely reduced LV function was comparable to patients with preserved LV [6]. However, a recent paper by Pascual

et al. showed that patients in the LVEF > 30% group had better clinical outcomes [10]. Percutaneous edge-to-edge repair for functional MR was recently implemented in the American Heart Association 2020 clinical guidelines [11]. However, it is still not clear how effective it is for patients with a severe reduction in LV function. While the positive value of MitraClip implantation on outcomes in chronic severe symptomatic ischemic FMR was shown before [12], data regarding patients with severe acute ischemic FMR, who are generally not included in registries or in randomized trials, are lacking, especially in patients with severely reduced LV function.

Our group previously published two case series showing that the MitraClip procedure is safe in patients with pulmonary congestion due to severe functional MR complicating MI [13,14]. MR reduction was significant with favorable hemodynamics and clinical improvement. The mortality rate after 30 days was as low as 10%. A recent publication by our group showed that even patients in cardiogenic shock may benefit from percutaneous edge-to-edge repair [15].

However, it is unknown how effective the MitraClip procedure is in severe LV dysfunction patients in an acute setting.

## 2. Methods

The International Registry of MitraClip in Acute Mitral Regurgitation following acute myocardial infarction (IREMMI) was established to assess the safety and outcomes of patients who underwent MitraClip in an acute setting following MI. In this multinational, multicenter retrospective registry, we evaluated the short and intermediate outcomes based on left ventricle ejection fraction. The procedure was performed in 21 centers in Europe, North America and Israel using the MitraClip device (Abbott, Menlo Park, CA, USA).

### 2.1. Study Population

We included patients who were treated with the MitraClip device due to at least moderate to severe (3+) MR, within 90 days of acute myocardial infarction (MI) between January 2014 and January 2020. Although treated medically, patients remained symptomatic (NYHA class > 3) and were evaluated by a multidisciplinary team of a non-interventional cardiologist, an interventional cardiologist and a cardiothoracic surgeon. All patients were deemed to be high risk for surgery and therefore a MitraClip procedure was performed in order to allow recovery. Patients who were anatomically unsuitable for edge-to-edge mitral valve repair were excluded. We evaluated immediate, 3-month and 1-year outcomes in those patients

### 2.2. Echocardiographic Evaluation

The severity of MR, left ventricle ejection fraction (LVEF), pulmonary artery pressure (PAP) and Mitral valve (MV) gradient were measured and graded according to the American Society of Echocardiography guidelines [16–18]. The severity of MR was assessed with an integrated multiparametric visual evaluation tool in accordance with standard clinical practice (incorporating 2D, spectral and color Doppler images), using an ordinal scale (grading 0—no MR, 1+ mild MR, 2+ moderate MR, 3+ moderate to severe MR, 4+ severe MR). A transesophageal echocardiogram (TEE) was completed in all patients prior to the procedure. MR grade, Mitral valve area (MVA) and MV gradient, calcium at grasping area and coaptation features were assessed in order to evaluate MitraClip feasibility.

### 2.3. MitraClip

A MitraClip procedure was performed under general anesthesia; fluoroscopy and transesophageal echocardiography (TEE) were routinely used for guidance. After transseptal puncture, the delivery system was advanced to the left atrium (LA), LV and retracted back to grasp the anterior and posterior leaflets. Procedural success was defined as the successful grasping of the anterior and posterior leaflets together with a reduction of at

least two MR grades. V-wave and left atrial pressures (LAP) were measured and recorded immediately before and after MitraClip implantation.

#### 2.4. Outcomes

Procedural and clinical adverse events during follow-up were defined according to the Mitral Valve Academic Research Consortium (MVARC) [13]. Outcomes of interest were procedural success, safety, hospital discharge, clinical outcomes and hemodynamics. Acute procedural success was defined as successful implantation of one or more clips with a reduction of the MR to <2+. Safety outcomes included procedural and periprocedural complications, namely, clip detachment, cerebrovascular event, MI, bleeding requiring transfusion and cardiac tamponade and urgent cardiovascular surgery. Clinical outcomes included weaning from mechanical ventilation and/or an LV support device and an NYHA class at follow-up. Hemodynamic parameters, LAP and V-wave were measured during the procedure. In cases where right heart catheterization was used, pulmonary artery wedge pressure (PCWP) was measured simultaneously with the procedure. After discharge, patients were followed up by individual centers in outpatient clinic visits in which clinical evaluation and echocardiography were performed.

#### 2.5. Statistical Analysis

Our analyses were performed using the entire cohort, drawing comparisons between patients with EF lower or higher than 35%. Patient characteristics are reported according to variable properties.

Categorical variables (ex. MR grade) are reported as % (*n*), and differences between subgroups were tested, when appropriate, using the chi-square test of Fischer's exact test. Continuous variables (ex. LVEF, PCWP, V-wave, sPAP) are reported according to their distribution. Those with a normal distribution are reported as mean ( $\pm$ standard deviation), and differences between subgroups were tested using the student's T-test. Those without a normal distribution are reported as median (interquartile range), and differences between subgroups were tested using the Mann-Whitney U. A p-value less than 0.05 was considered to be statistically significant. Kaplan-Meier estimates were used to calculate survival curves, which were adjusted to age and compared using the log-rank test. All clinical events were analyzed by time-to first event for Kaplan-Meier analysis. The IBM Statistical Package for the Social Sciences (SPSS) Statistics 26.0 (IBM Corp., Armonk, NY, USA) was utilized to perform the analyses.

### 3. Results

From January 2014 to January 2020, 105 patients were included in the registry.

#### 3.1. Patient Characteristics

The mean age of patients was  $70.5 \pm 10.3$  years and 50% were female. All patients had at least MR grade 3 before the intervention. Patients suffered pulmonary congestion despite initial medical therapy, including intravenous diuretics. Of the patients, 52 (55%) were in cardiogenic shock and were further supported by an intra-aortic balloon pump (IABP) or intravenous vasopressors, whilst 41 patients (43%) required mechanical ventilation unrelated to the procedure. The patient population was divided into two groups based on the median LVEF of 35%. The LVEF < 35% group included 47 patients, whilst LVEF  $\geq$  35% included 58 patients with a mean LVEF of  $26 \pm 6\%$  and  $44 \pm 9\%$ ,  $p < 0.01$ , respectively.

Baseline characteristics are listed in Table 1. Patients in the LVEF < 35% group were younger when compared to patients with LVEF  $\geq$  35% ( $68.4 \pm 9.1$  vs.  $72.4 \pm 11.0$ ,  $p = 0.05$ ), as well as having a higher body-mass index (BMI) ( $27.9 \pm 4.7$  vs.  $25.5 \pm 5.3$ ,  $p = 0.04$ ). There was no difference in other risk factors for cardiovascular disease, past MI, past Coronary Artery Bypass Graft (CABG) or in the surgical risk assessment by Euroscore II.

**Table 1.** Baseline Patient Characteristics.

| Parameter                       |                          | 1                | 2           |             |         |
|---------------------------------|--------------------------|------------------|-------------|-------------|---------|
|                                 |                          | Total Population | LVEF < 35%  | LVEF ≥ 35%  | p-Value |
| n                               |                          | 105              | 47          | 58          |         |
| Demographics                    |                          |                  |             |             |         |
| Age, years                      |                          | 70.5 ± 10.3      | 68.4 ± 9.1  | 72.4 ± 11.0 | 0.05    |
| Sex, Female, % (n)              |                          | 50 (53)          | 43 (20)     | 57 (33)     | 0.17    |
| BMI (Kg/M <sup>2</sup> )        |                          | 26.5 ± 5.2       | 27.9 ± 4.7  | 25.5 ± 5.3  | 0.04    |
| Hypertension, % (n)             |                          | 70.5 (74)        | 68.1 (32)   | 70.7 (41)   | 0.83    |
| Diabetes, % (n)                 |                          | 45.7 (48)        | 51.1 (24)   | 41.4 (24)   | 0.33    |
| Dyslipidemia, % (n)             |                          | 62.9 (66)        | 70.0 (31)   | 60.3 (35)   | 0.69    |
| COPD, % (n)                     |                          | 17.1 (18)        | 19.1 (9)    | 15.5 (9)    | 0.80    |
| CKD ≥ grade 2, % (n)            |                          | 29.5 (31)        | 25.5 (12)   | 32.8 (19)   | 0.82    |
| Prior stroke, % (n)             |                          | 13.3 (14)        | 6.4 (3)     | 19.0 (11)   | 0.08    |
| Prior MI, % (n)                 |                          | 55.2 (58)        | 61.7 (29)   | 50 (29)     | 0.24    |
| Prior CABG, % (n)               |                          | 26.7 (28)        | 23.4 (11)   | 29.3 (17)   | 0.51    |
| Euroscore 2, %                  |                          | 17.2 ± 16.7      | 20.1 ± 18.5 | 14.9 ± 15.0 | 0.14    |
| Presentation                    |                          |                  |             |             |         |
| STEMI, % (n)                    |                          | 71.4 (75)        | 66.0 (31)   | 75.9 (44)   | 0.25    |
| Killip Class 3+, % (n)          |                          | 68.6 (72)        | 78.7 (37)   | 60.3 (35)   | 0.06    |
| Echocardiographic               |                          |                  |             |             |         |
| MR Grade 4+, % (n)              |                          | 81.0 (85)        | 83.0 (39)   | 79.3 (46)   | 0.80    |
| Papillary muscle rupture, % (n) |                          | 5.7 (6)          | 2.1 (1)     | 8.6 % (5)   | 0.22    |
| Ejection Fraction (%)           |                          | 35.8 ± 11.9      | 25.8 ± 5.7  | 44 ± 8.9    | <0.01   |
| sPAP, mmHg                      |                          | 53.6 ± 18.6      | 54.4 ± 16.1 | 53.1 ± 20.3 | 0.75    |
| Coronary Angiography            |                          |                  |             |             |         |
| Multivessel disease, % (n)      |                          | 80 (84)          | 83.0 (39)   | 77.6 (45)   | 0.63    |
| Infarct Related Artery (IRA)    | RCA, % (n)               |                  | 11 (5)      | 41 (24)     | <0.01   |
|                                 | LCX, % (n)               |                  | 32 (15)     | 33 (19)     |         |
|                                 | LAD, % (n)               |                  | 53 (25)     | 22 (13)     |         |
|                                 | PCI, % (n)               | 94.3 (99)        | 95.7 (45)   | 95.7 (54)   |         |
| Wall Involved                   | Anterior                 |                  | 51 (24)     | 19 (11)     | <0.01   |
|                                 | Inferior                 |                  | 30 (14)     | 59 (34)     |         |
|                                 | Lateral and/or Posterior |                  | 19 (9)      | 22 (13)     |         |
| ICCU Status and Treatment       |                          |                  |             |             |         |
| Cardiogenic Shock               |                          | 54.3 (57)        | 63.8 (30)   | 46.6 (27)   | 0.12    |
| Mechanical Ventilation          |                          | 42.9 (45)        | 46.8 (22)   | 39.7 (23)   | 0.55    |
| Vasoactive medication           |                          | 42.9 (45)        | 48.9 (23)   | 37.9 (22)   | 0.32    |
| Any MSD                         |                          | 37.1 (39)        | 42.6 (20)   | 32.8 (19)   | 0.32    |

Abbreviations: BMI—Body Mass Index; CABG—Coronary Artery Bypass Grafting; CAD—Coronary Artery Disease; CKD—Chronic Kidney Disease; COPD—Chronic Obstructive Lung Disease; Euroscore II—European System for Cardiac Operative Risk Evaluation; ICCU—Intensive Coronary Care Unit; LAD—Left Anterior Descending; LCX—Left Circumflex; LVEF—Left Ventricle Ejection Fraction; MSD—Mechanical Support Device; PCI—Percutaneous Coronary Intervention; RCA—Right Coronary Artery; sPAP—Systolic Pulmonary artery pressure; STEMI—ST Elevation myocardial infarction.

Out of 105 patients, 75 presented with STEMI but there was no significant difference between the two groups (66% vs. 76%, respectively,  $p = 0.14$ ). In both groups there was a high rate of multi-vessel disease (80% vs. 78%,  $p = 0.63$ ). The common infarct related artery (IRA) was the LAD in the LVEF < 35% group (53% vs. 22%), and the RCA in the LVEF ≥ 35% group (41% vs. 11%,  $p < 0.01$ ).

The anterior LV wall was involved in 51% of patients in the LVEF < 35% group vs. 19% of patients in the LVEF ≥ 35% group. Accordingly, the inferior wall was more involved in the LVEF ≥ 35% group (59% vs. 30%,  $p < 0.01$ ).

### 3.2. Procedural and Safety Outcomes

Procedure characteristics, safety and outcomes are listed in Table 2.



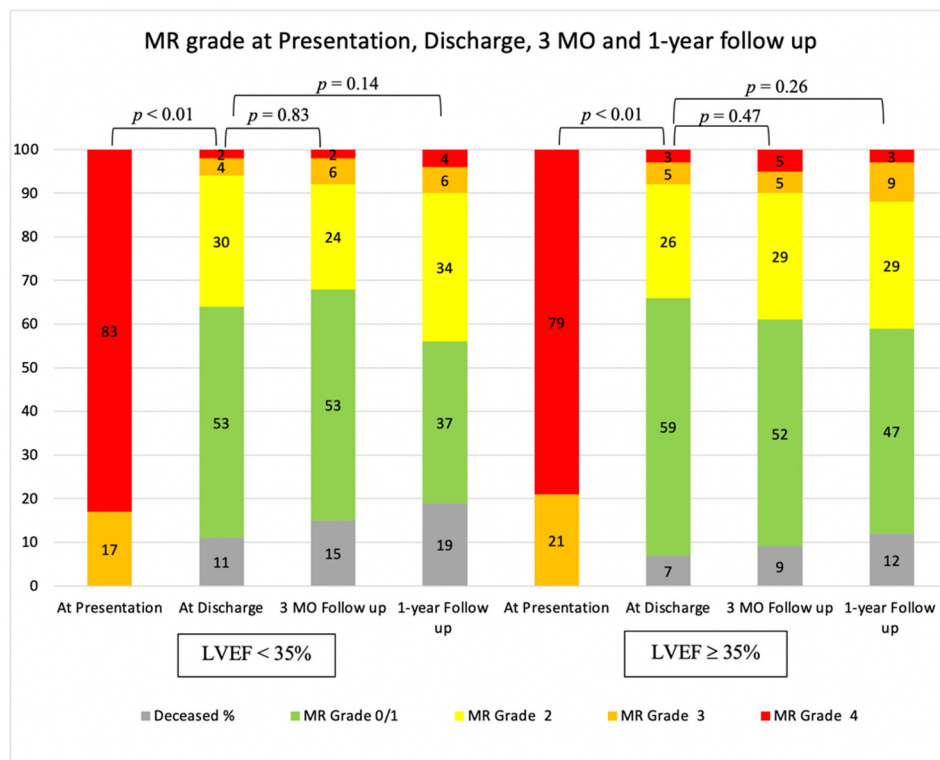
**Table 2.** Procedure and Outcomes.

| Parameter                           |                  | 1          | 2          |                 |
|-------------------------------------|------------------|------------|------------|-----------------|
|                                     | Total Population | LVEF < 35% | LVEF ≥ 35% | <i>p</i> -Value |
| <i>n</i>                            | 105              | 47         | 58         |                 |
| Procedure                           |                  |            |            |                 |
| Procedure Time, min                 | 115 ± 90         | 122 ± 84   | 109 ± 95   | 0.51            |
| Major Complications                 | 6.7 (7)          | 8.5 (4)    | 5.2 (3)    | 0.70            |
| MI to Procedure, days               | 27 ± 22          | 35 ± 26    | 20 ± 17    | <0.01           |
| Clips Implanted, mean               | 1.7 ± 0.7        | 1.8 ± 0.7  | 1.6 ± 0.6  | 0.22            |
| MR > 2 at discharge, % ( <i>n</i> ) | 8.6 (9)          | 8.5 (4)    | 8.6 (5)    | 1               |
| MV Gradient post                    | 3.7 ± 1.7        | 3.7 ± 1.6  | 3.7 ± 1.8  | 0.91            |
| Outcomes                            |                  |            |            |                 |
| Procedure success                   | 91.4 (96)        | 93.6 (44)  | 89.7 (52)  | 0.73            |
| In hospital mortality               | 8.6 (9)          | 10.6 (5)   | 6.9 (4)    | 0.51            |
| Major Complications                 | 6.7 (7)          | 8.5 (4)    | 5.2 (3)    | 0.70            |
| Mortality at 3 months               | 11.4 (12)        | 14.9 (7)   | 8.6 (5)    | 0.50            |
| Rehospitalizations at 3 months      | 13.3 (14)        | 19.1 (9)   | 15.5 (9)   | 0.77            |
| 1-year mortality                    | 15.2 (16)        | 19.1 (9)   | 12.1 (7)   | 0.49            |

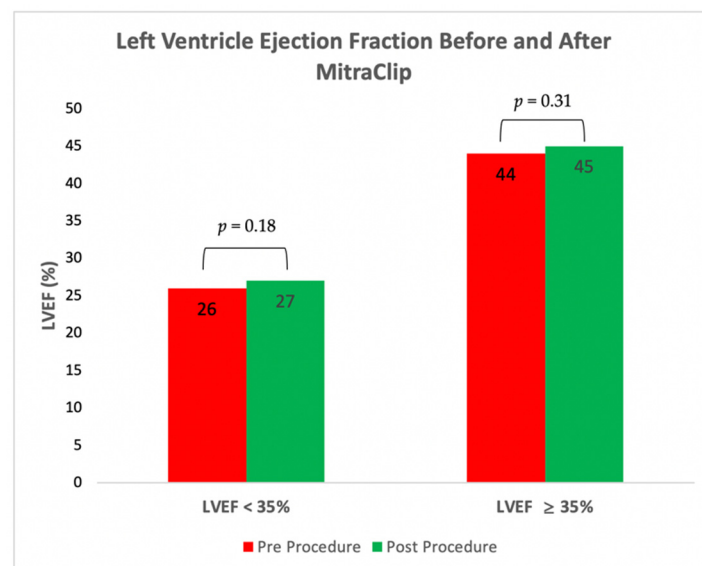
Abbreviations: LVEF—Left Ventricle Ejection Fraction; MI—Myocardial Infarction; MO—Month; MR—Mitral Regurgitation; MV—Mitral Valve.

A MitraClip procedure was performed, on average,  $27 \pm 22$  days after the date of the index MI. When drawing comparisons based on LVEF, procedures were delayed in the  $\text{LVEF} \geq 35\%$  group, where the MitraClip procedure was performed, on average, at  $37 \pm 26$  days vs.  $21 \pm 18$  days,  $p = 0.001$  in the  $\text{LVEF} < 35\%$  group. Procedure success was 91.4% (96 out of 105 patients). There was no significant difference between the two LVEF groups, 96% vs. 90%,  $p = 0.73$ . The procedure's mean duration was  $115 \text{ min} \pm 90 \text{ min}$ . There was no difference in duration between the  $\text{LVEF} < 35\%$  group ( $122 \text{ min} \pm 84 \text{ min}$ ) and the  $\text{LVEF} \geq 35\%$  group ( $109 \text{ min} \pm 95 \text{ min}$ ),  $p = 0.51$ . MR reduction to grade 1 was achieved in 64 patients and to 2+ in 32 patients (Figure 1). The grade of MR significantly decreased after the procedure,  $p < 0.01$ . No difference was observed between the two LV groups. One to four clips were implanted in each case; 42 patients were implanted with a single clip, 52 were implanted with two clips, 9 were implanted with three clips and one patient was implanted with four clips. The mean mitral valve gradient was  $3.7 \text{ mmHg} \pm 1.7$  and there was no significant difference based on LVEF.

Hemodynamic features from presentation to discharge were improved in both groups. Left atrial V-Wave was reduced from  $45.1 \pm 15.9 \text{ mmHg}$  to  $20.2 \pm 7.0 \text{ mmHg}$ ,  $p < 0.01$  in the  $\text{LVEF} < 35\%$  group and from  $31.3 \pm 17.1 \text{ mmHg}$  to  $17.1 \pm 5.7 \text{ mmHg}$ ,  $p < 0.01$ , in the  $\text{LVEF} \geq 35\%$  group (Figure 2a). There was no significant change in EF from presentation to discharge in either group (26% to 27%,  $p = 0.18$  and 44% to 45%,  $p = 0.31$ , respectively) (Figure 2b). SPAP reduction was observed in both groups from presentation to discharge ( $54.1 \pm 14.8 \text{ mmHg}$  to  $43.9 \pm 16.3 \text{ mmHg}$ ,  $p < 0.01$ , in the  $\text{LVEF} < 35\%$  group and from  $52.9 \pm 22.8 \text{ mmHg}$  to  $41.7 \pm 21.7 \text{ mmHg}$ ,  $p < 0.01$ , in the  $\text{LVEF} \geq 35\%$  group) (Figure 3a). Major complications following the procedure were relatively low in both groups (7% vs. 9%,  $p = 0.70$ ).

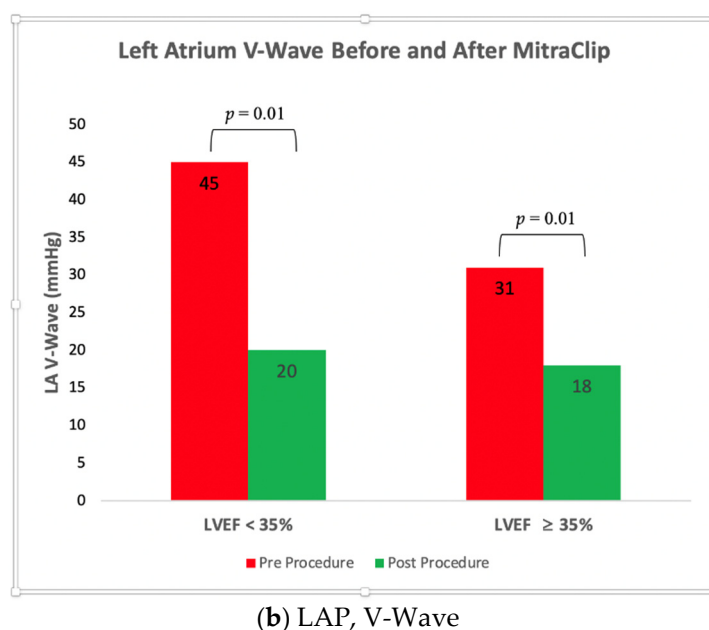


**Figure 1.** MR grades at presentation, discharge, 3-month and 1-year follow-up. MR was significantly reduced from presentation to discharge in both LVEF groups. MR reduction remains consistent after discharge and throughout follow-up in both groups.



**(a) LVEF**

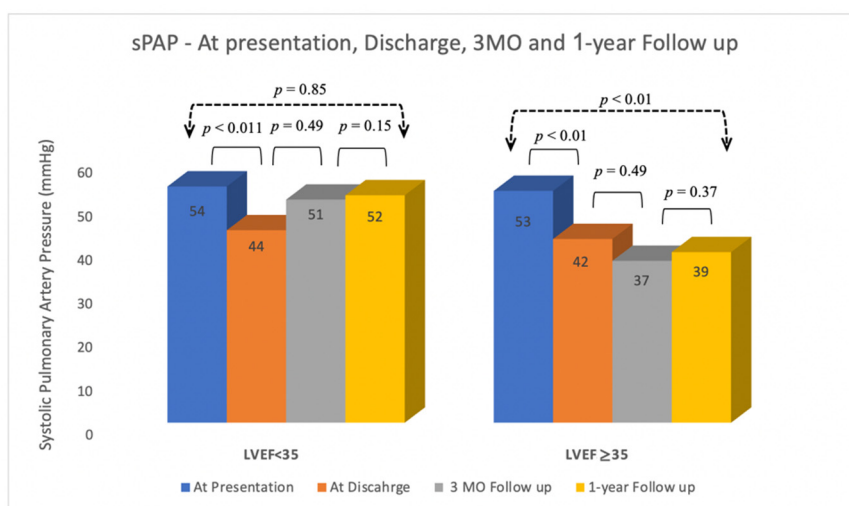
**Figure 2. Cont.**



**Figure 2.** Left Ventricle Ejection Fraction (LVEF) and Left Atrial Pressure (LAP) before and after the procedure. (a) There was no significant change in Left ventricle ejection fraction (LVEF) before and after MitraClip procedure in both LVEF < 35% and LVEF ≥ 35% groups; (b) There was a significant reduction in LAP before and after MitraClip procedure in both LVEF < 35% and LVEF ≥ 35% groups.

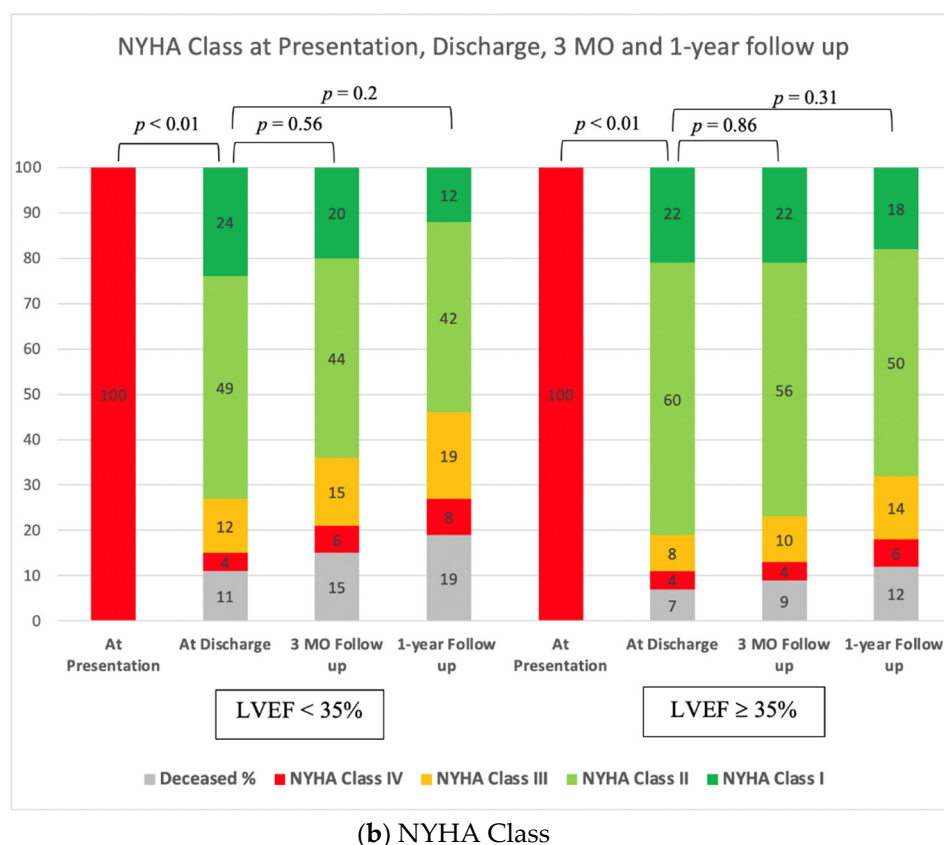
### 3.3. Mortality Analysis

In-hospital mortality was low in both the LVEF < 35% and LVEF ≥ 35% groups (11% vs. 7%,  $p = 0.51$ ). One-year mortality was also low and non-significant when comparing the two groups (19% vs. 12%,  $p = 0.49$ ). Age-adjusted survival curves for mortality are shown in Figure 4. There was no significant difference between the two groups at the 1-year follow-up (Log Rank,  $p = 0.221$ ).



**Figure 3.** Cont.





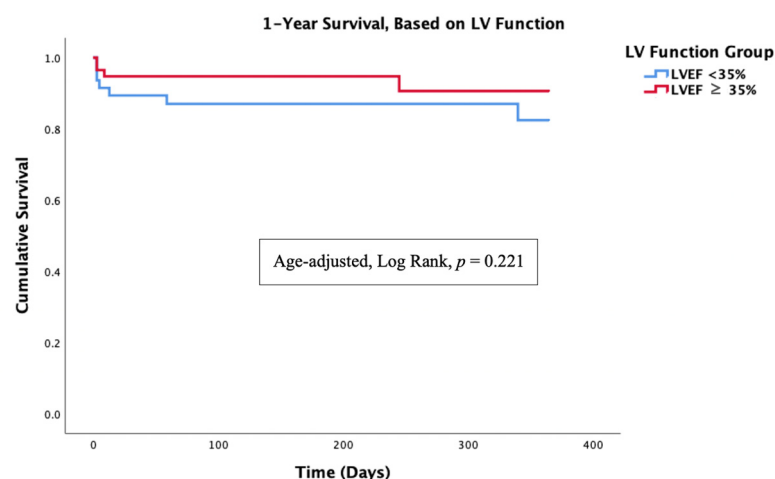
**Figure 3.** Clinical and Echocardiographic evaluation at presentation, discharge, 3-month and 1-year follow-up. (a) Systolic Pulmonary Artery Pressure (sPAP) was significantly reduced from presentation to discharge in both LVEF groups. sPAP reduction from presentation to 1-year follow up was consistent only for patients in the LVEF > 35%. (b) NYHA class was significantly improved from presentation to discharge in both LVEF groups. NYHA class improvement remain consistent throughout follow-up in both groups; 36 out of 42 patients in the LVEF < 35% group and 51 out of 54 patients in the LVEF ≥ 35% group had NYHA functional class I or class II at 3-month follow up.

### 3.4. Follow-Up

The median follow-up period was 12 months (IQR 6 to 21).

Follow-up echocardiography after the procedure demonstrated non-significant change in MR from discharge to 3-month and 1-year follow up (Figure 1). This may indicate the durability of the MitraClip procedure, regardless of LV function. Patients benefited from a considerable improvement in functional capacity after the procedure. This improvement was observed throughout the follow-up period (Figure 3b).

As mentioned, significant reduction in sPAP was achieved in both groups after the procedure. During follow-up (3-month and 1-year), there was no significant change in sPAP between the two groups. However, when comparing the pre-procedure sPAP with 1-year sPAP, patients in the LVEF < 35% group did not benefit from sustainable reduction (54 mmHg and 52 mmHg,  $p = 0.85$ ), as opposed to patients in the LVEF ≥ 35% group (53 mmHg to 39 mmHg,  $p < 0.01$ ). This change in hemodynamics between the groups was not translated to a change in functional class at 3-month and 1-year follow-up. Rehospitalization rates at 3-month follow-up were also comparable (19% vs. 16%,  $p = 0.77$ ).



| Number at Risk | 0  | 3-Month | 6-Month | 9-Month | 1-Year |
|----------------|----|---------|---------|---------|--------|
| LVEF < 35%     | 47 | 35      | 32      | 30      | 25     |
| LVEF ≥ 35%     | 58 | 43      | 40      | 38      | 31     |

**Figure 4.** Kaplan-Meier curve for survival, based on LVEF. Left Ventricle Ejection Fraction (LVEF) was not associated with lower or higher mortality rate, Log Rank,  $p = 0.221$ .

#### 4. Discussion

In this international multicenter study, we collected the largest published series of patients who underwent the MitraClip procedure after acute MI complicated by severe MR. We aimed to compare the feasibility of PMVR in patients according to their EF.

There were few significant differences in the basic characteristics between the two EF groups, namely, age and BMI. Almost half of patients required mechanical support and/or were treated with inotropes. In the majority of patients, the salvage MitraClip procedure significantly decreased the MR, as well as the pulmonary hypertension and left atrial V wave; this therefore allowed recovery. Procedural complications were rare, and the clinical condition of most patients was significantly improved as a result of the mitral valve repair. The clinical benefit was maintained through follow up evaluation.

Primary mitral regurgitation in the acute setting is usually due to complete or partial papillary muscle rupture, secondary to ischemia or necrosis, resulting in prolapse or flail leaflet. This condition is accompanied with rapid deterioration and often requires urgent intervention.

Ischemic MR is caused by left ventricular global or regional pathological remodeling due to acute or chronic coronary artery disease [19]. The prevalence of this condition varies between studies and reaches 50% of all MI patients in some series [20]. MR is a central component of the vicious cycle of LV remodeling and HF in MI patients. The regurgitation raises the volume overload and ventricular wall stress, causing further LV dilatation that worsens the MR [19]. Solid data suggests that FMR on presentation, or persistent ischemic FMR, is a negative prognostic factor that is associated with worsened short-term and long-term prognosis [20,21].

Ischemic FMR occurs more frequently with inferior infarction due to geometric distortion in the region of the papillary muscle [22]. Interestingly, in our cohort, 50% of patients presented with anterior MI, suggesting that FMR that is associated with anterior wall infarctions is more likely to require salvage mitral valve intervention. A possible explanation for this is that an anterior wall MI involves more dysfunctional LV and a larger infarct size that causes apical tethering of the valve compared with the localized infarction of the inferior wall. Indeed, MR complicating anterior STEMI was shown to be associated with worse short-term and long-term outcomes than inferior wall infarct [23]. Previous

studies have shown that patients at higher risk of developing ischemic FMR are elderly females who have lower EF and multi-vessel CAD [24]. It is reasonable to assume that EF is an important predictor of outcomes after MI and, indeed, data from the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry [25] suggests that EF is directly associated with outcomes among patients after MI: the risk of 1-year mortality was 29.0% in patients with  $EF \leq 35\%$ , compared with 13.0% in patients with  $EF \geq 55\%$ . On the other hand, Gerber et al. evaluated the prognostic impact of HF after MI in more than 2500 patients and found that mortality was related to HF but did not differ by EF [26].

In the German transcatheter mitral valve interventions (TRAMI) registry, patients were divided into three groups:  $LVEF < 30\%$ ,  $LVEF 30\text{--}50\%$  and  $LVEF > 50\%$ . It was concluded that the clinical benefit to patients with severely reduced LV function was comparable to patients with preserved LV. In this registry, over 80% of patients in the  $LVEF < 30\%$  had functional MR<sup>6</sup>. In a recent study published by Pascual et al., patients were divided according to LVEF above and below 30% and showed that patients in the  $LVEF > 30\%$  group had better clinical outcomes [10].

We found that patients with severe acute MR and  $LVEF < 35\%$  had similar mortality rates to patients with  $LVEF \geq 35\%$ . This finding may suggest that, rather than low EF, severe acute MR is the dominant factor in deterioration and clinical instability and should therefore be treated regardless of EF. However, we cannot exclude that the similar survival rates were related to a lack of statistical power. Revascularization for acute MI can provide improvement of LV function and may decrease the ischemic FMR. Nishino et al. showed that shorter reperfusion time and successful revascularization at presentation were the independent predictors of improvement in FMR [21]. The Acute Myocardial Infarction Contrast Imaging (AMICI) multicenter study showed that a short time to revascularization ( $< 2.5$  h) independently predicts reverse remodeling which affects the magnitude of FMR [27].

While the negative prognostic effect of ischemic FMR is well recognized, the impact of surgical repair of MR on LV remodeling and outcomes is still controversial, especially in patients with severely reduced LV function, who are poor candidates for surgery [28–30]. Theoretically, the less invasive MitraClip procedure may be considered as an alternative to surgery in high-risk patients. In fact, recent trials suggest that MitraClip therapy improves quality of life and may even reduce mortality among patients with severe chronic ischemic MR [4,6]. However, in most of these clinical trials, patients who had acute or subacute MR due to a recent MI were excluded.

The impact of MitraClip in an acute setting was initially only evaluated in case reports and a small case series [31–34]. The two largest case series were previously published by our group [13,14]. Our findings confirm that MitraClip is a safe and effective procedure in acute settings for a selected high-risk group, both with  $LVEF < 35\%$  and  $LVEF \geq 35\%$ , and that in most of the patients the effectiveness of mitral intervention was sustainable in long term follow up.

The study has several limitations that merit consideration. First, although several centers were involved, the sample size is relatively small, and the results should be interpreted with caution. Second, our analysis used retrospectively analyzed observational data and therefore the associations between baseline characteristics and outcomes may be confounded by unmeasured variables. Third, in all our cases, MitraClip was performed as a salvage procedure in acutely ill patients. Therefore, the findings cannot be generalized for stable patients who develop ischemic FMR after MI.

Large, multicenter and randomized trials are needed to confirm this data among acute ischemic FMR.

## 5. Conclusions

MitraClip intervention in patients with acute severe FMR due to a recent MI in an acute setting is safe and feasible. Even patients with severe LV dysfunction may benefit from transcatheter mitral valve intervention and should not be excluded.

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**Data Availability Statement:** The data that supports the findings of this study are available from the corresponding author, D.H., upon reasonable request.

**Conflicts of Interest:** Dan Haberman is an Abbott CEC member. Rodrigo Estévez-Loureiro, Dabit Arzamendi, Paolo Denti, Xavier Freixa, are consultants for Abbott. Andrew Czarnecki received speaker fee from Abbott and consultant for Caisson Interventional and Baylis Medical. Marco Gennari is consultant for Medtronic. Luis Nombela-Franco has served as a proctor of Abbott Vascular and received speakers' honoraria from Boston Scientific and Abbott Vascular. Francesco Maisano has served as a consultant for Abbott Vascular, Edwards Lifesciences, Cardiovalve, Valtech, and Medtronic; and is cofounder of 4tech. Maurizio Taramasso is Consultant for Abbott, Boston Scientific, 4tech and receives personal fees from Edwards Lifescience, CoreMedic, Swissvortex and Mitraltech. Mony Shuvy is a proctor and consultant for Abbott and consultant for Edwards Lifesciences. All other authors have reported that they have no relationship relevant to the contents of this paper to disclose.

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## 10.7. Anexo 7

Prognostic role of TAPSE to PASP ratio in patients undergoing MitraClip procedure.

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Article

# Prognostic Role of TAPSE to PASP Ratio in Patients Undergoing MitraClip Procedure

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**Abstract:** Background: Transcatheter mitral valve repair (TMVR) is an effective therapy for high-risk patients with severe mitral regurgitation (MR) but heart failure (HF) readmissions and death remain substantial on mid-term follow-up. Recently, right ventricular (RV) to pulmonary arterial (PA) coupling has emerged as a relevant prognostic predictor in HF. In this study, we aimed to assess the prognostic value of tricuspid annular plane systolic excursion (TAPSE) to PA systolic pressure (PASP) ratio as a non-invasive measure of RV-to-PA coupling in patients undergoing TMVR with MitraClip (Abbott, CA, USA). Methods: Multicentre registry including 228 consecutive patients that underwent successful TMVR with MitraClip. The sample was divided in two groups according to TAPSE/PASP median value: 0.35. The primary combined endpoint encompassed HF readmissions and all-cause mortality. Results: Mean age was  $72.5 \pm 11.5$  years and 154 (67.5%) patients were male. HF readmissions and all-cause mortality were more frequent in patients with  $\text{TAPSE/PASP} \leq 0.35$ : Log-Rank 8.844,  $p = 0.003$ . On Cox regression, TAPSE/PASP emerged as a prognostic predictor of the primary combined endpoint, together with STS-Score. TAPSE/PASP was a better prognostic predictor than either TAPSE or PASP separately. Conclusions: TAPSE/PASP ratio appears as a novel prognostic predictor in patients undergoing MitraClip implantation that might improve risk stratification and candidate selection.

**Keywords:** MitraClip; mitral valve repair; mitral valve regurgitation; pulmonary hypertension; right ventricular to pulmonary arterial coupling; transthoracic echocardiography

## 1. Introduction

Over the past decade, transcatheter mitral valve repair (TMVR) with the MitraClip system (Abbott; Menlo Park, California, USA) has proven a safe and effective treatment alternative for high-risk patients with severe mitral regurgitation (MR) [1–4].

Currently, the indication for TMVR with the MitraClip system as an alternative to surgery is set by a dedicated Heart Team, after a thorough evaluation of each individual case, including appropriateness and feasibility of the procedure, risk stratification and benefit prediction [5,6]. This decision-making process is supported by surgical risk models, which have, however, exhibited limited accuracy in patients undergoing TMVR with MitraClip [2,7]. In addition, relevant prognostic indicators identified by prior studies in this population are also taken into account [8–11]. Notwithstanding, heart failure (HF) readmissions and death during the first year after MitraClip implantation remain substantial [2,3,8–11], even after a successful procedure. Thus, refinement of current prognostic predictors to improve candidate selection and avoid futility remains an important unanswered question.

Patients with severe MR considered for a MitraClip procedure often associate pulmonary hypertension (PH) and right ventricular (RV) dysfunction, which are indicators of a worse outcome [12–14]. Indeed, many patients are declined a MitraClip procedure due to PH and RV dysfunction, but TMVR may still provide clinical benefit in selected patients and has been associated with a significant reduction in pulmonary pressures and RV reverse remodelling in several studies [14–16].

Recently, RV to pulmonary arterial (PA) coupling has emerged as a relevant prognostic indicator in HF and PH [17–19]. RV-PA coupling quantifies the adaptation of the RV to its afterload and has the ability to detect pending RV failure [17–20]. In clinical practice, RV to PA coupling is frequently assessed non-invasively by means of the ratio between tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP) [19–22]. However, the prognostic role of TAPSE/PASP ratio in patients undergoing MitraClip implantation has not been evaluated to date.

In this study we aimed to assess the ability of baseline TAPSE/PASP ratio to improve prognostic stratification in patients undergoing successful TMVR with MitraClip.

## 2. Materials and Methods

### 2.1. Study Design and Population

228 consecutive patients undergoing TMVR with MitraClip between June 2012 and June 2018 at 17 Spanish centres were included.

Patients' data were obtained from the Spanish MitraClip observational multicentre Registry, endorsed by the Cardiac Catheterization and Interventional Cardiology Section of the Spanish Society of Cardiology. The sample included patients with primary and secondary MR graded as moderate to severe (3+) or severe (4+) on pre-procedural echocardiography. Only patients that displayed persistent HF symptoms despite optimized guideline directed medical therapy were included. At each of the centres, the corresponding Heart Team established the indication of TMVR with MitraClip as the best treatment alternative, after careful evaluation of each case. Follow-up data were prospectively collected at each participating center by serial clinical, analytical and echocardiographic evaluations. Only patients with a comprehensive baseline echocardiographic examination that underwent successful TMVR with residual MR grade  $\leq 2+$  were included in the current analysis.

The Ethics Committee of each of the participating centres approved the Study Protocol and all patients provided written informed consent prior to their enrolment.

### 2.2. Echocardiography Parameters

MR severity was graded as none, mild (1+), moderate (2+), moderate to severe (3+) and severe (4+) according to regurgitant volume and effective regurgitant orifice area. TAPSE was measured as the peak excursion of the tricuspid annulus from end-diastole to end-systole in the apical 4-chamber view with the M-mode. RV systolic pressure was determined from the peak velocity of the tricuspid regurgitation (TR) jet using the simplified Bernoulli equation. Right atrial pressure was estimated by the diameter and collapsibility of the inferior vena cava and added to the calculated gradient to yield PASP. Echocardiography measurements were recorded and averaged over three consecutive heart cycles in patients in sinus rhythm and over 3–5 heart cycles in patients in atrial fibrillation.

### 2.3. Right Heart Catheterization

Right heart catheterization (RHC) was performed via femoral or brachial vein employing standard methodology in a small subset of the total sample, at the discretion of the patient's physician and standard hemodynamic measurements were registered.

### 2.4. Definitions and Outcomes

The details of the mitral repair procedure have been previously described [1]. All procedures were guided by transesophageal echocardiography. Procedural success was defined as a reduction in the degree of MR equal to or less than moderate  $\leq 2+$ . Functional class was defined according to the New York Heart Association (NYHA) classification and was assessed at baseline and during follow-up.

The primary combined endpoint was defined as the composite of HF readmissions and all-cause death during the first-year post-procedure, including in-hospital mortality. Secondary endpoints consisted of the occurrence of each of these events separately. Follow-up for HF hospitalizations began after discharge from index admission.

Periprocedural complications and in-hospital and thirty-day outcomes were defined as per Mitral Valve Academic Research Consortium criteria [23] and encompassed pericardial effusion, air embolism, cordal rupture, catheter thrombosis, clip detachment, bleeding assessed according to Bleeding Academic Research Consortium (BARC) criteria, access-site vascular complications, myocardial infarction, acute kidney injury, pulmonary embolism, stroke, in-hospital mortality and 30-day readmission for decompensated HF.



### 2.5. Statistical Analysis

Categorical variables were expressed as frequencies and percentages and continuous variables as mean  $\pm$  standard deviation. The sample was divided in two groups according to the median value of baseline TAPSE/PASP ratio.

Comparisons between patient's groups according to TAPSE/PASP ratio or event status were made by  $\chi^2$  test, unpaired Student's *t*-test and Mann–Whitney U-test, as appropriate.

Survival curves for baseline TAPSE/PASP were constructed with the Kaplan–Meier method and compared with the Log-Rank test. A multivariate Cox regression model was performed, including all variables with a *p*-value  $\leq 0.10$  on univariate analysis as well as variables expected to influence outcome based on previous publications, after exclusion of colinearity. Discrimination measures by means of Harrell's C-statistics were calculated for Cox regression model and the proportional hazard assumption for exposure of variables included in the model was verified.

Correlation analysis was performed by means of Pearson correlation coefficient to assess for the existence of a linear relationship between baseline TAPSE/PASP ratio and other hemodynamic parameters.

A *p*-value  $< 0.05$  was considered statistically significant for all tests. Statistical analyses were performed with SPSS 21.0 (IBM, Chicago, IL, US) for Windows.

### 3. Results

A total of 228 consecutive patients were included in our study. Mean age was  $72.5 \pm 11.5$  years and 154 (67.5%) patients were male. The vast majority of patients were highly symptomatic at baseline (NYHA functional class  $\geq$  III/IV, 86.8%) and surgical risk was moderately increased (mean STS  $5.8 \pm 5.3$ , mean EuroSCORE-II  $8.5 \pm 7.9$ ). MR was severe in 187 (82.1%) patients and moderate-severe in the remainder 41 (17.9%) cases. The underlying MR aetiology was classified as secondary in 147/225 (65.3%) patients, primary in 50/225 (22.2%) cases, mixed aetiology in 28/225 (12.3%) and was not reported in 3 cases. All patients underwent successful TMVR with the MitraClip device with  $1.5 \pm 0.6$  clips on average. Postprocedural MR was reduced to grade 0–1+ in 147 (64.5%) patients and to grade 2+ in the rest.

#### 3.1. Baseline Characteristics According to TAPSE/PASP Values

Median value of TAPSE/PASP was 0.35, with lower values indicating RV to PA uncoupling, in agreement with cutoff values with prognostic implications reported in prior studies in HF [19,20,24,25]. Patients with TAPSE/PASP ratio  $\leq 0.35$  presented a higher prevalence of grade 3–4+ TR, lower TAPSE, greater PASP and higher left atrial (LA) v-wave and PASP values determined by RHC, Table 1. No further differences in baseline characteristics according to TAPSE/PASP ratio existed.

**Table 1.** Baseline characteristics according to TAPSE/PASP.

|                                                          | TAPSE/PASP $\leq 0.35$<br>( <i>n</i> = 114) | TAPSE/PASP $> 0.35$<br>( <i>n</i> = 114) | Total Sample<br>( <i>n</i> = 228) | <i>p</i> -Value |
|----------------------------------------------------------|---------------------------------------------|------------------------------------------|-----------------------------------|-----------------|
| <b>Clinical Characteristics</b>                          |                                             |                                          |                                   |                 |
| Age (years)                                              | $71.8 \pm 11.8$                             | $73.3 \pm 11.2$                          | $72.5 \pm 11.5$                   | 0.327           |
| Sex, male ( <i>n</i> , %)                                | 81(71.1)                                    | 73(64)                                   | 154(67.5)                         | 0.258           |
| Hypertension ( <i>n</i> , %)                             | 79(69.3)                                    | 86(76.1)                                 | 165(72.7)                         | 0.250           |
| Diabetes mellitus ( <i>n</i> , %)                        | 40(35.1)                                    | 34(29.8)                                 | 74(32.5)                          | 0.396           |
| Atrial fibrillation ( <i>n</i> , %)                      | 68(59.6)                                    | 65(58)                                   | 133(58.8)                         | 0.893           |
| Glomerular filtration rate (mL/min/1.73 m <sup>2</sup> ) | $58.2 \pm 24.8$                             | $64 \pm 26.1$                            | $60.9 \pm 25.4$                   | 0.164           |
| Stage 3b–5 chronic renal failure ( <i>n</i> , %)         | 42(36.8)                                    | 33(28.9)                                 | 75(32.9)                          | 0.205           |

Table 1. Cont.

|                                                                    | TAPSE/PASP $\leq 0.35$<br>( <i>n</i> = 114) | TAPSE/PASP $> 0.35$<br>( <i>n</i> = 114) | Total Sample<br>( <i>n</i> = 228) | <i>p</i> -Value |
|--------------------------------------------------------------------|---------------------------------------------|------------------------------------------|-----------------------------------|-----------------|
| <b>Clinical Characteristics</b>                                    |                                             |                                          |                                   |                 |
| Ischemic heart disease ( <i>n</i> , %)                             | 61(53.5)                                    | 52(45.6)                                 | 113(49.6)                         | 0.400           |
| Prior PCI ( <i>n</i> , %)                                          | 41(36)                                      | 35(30.7)                                 | 76(33.3)                          | 0.699           |
| Prior CABG ( <i>n</i> , %)                                         | 25(21.9)                                    | 17(14.9)                                 | 42(18.4)                          | 0.156           |
| Extra cardiac arteriopathy ( <i>n</i> , %)                         | 16(14)                                      | 19(16.7)                                 | 35(15.4)                          | 0.512           |
| Previous cardiac surgery ( <i>n</i> , %)                           | 38(33.3)                                    | 24(21.1)                                 | 62(27.2)                          | 0.113           |
| COPD ( <i>n</i> , %)                                               | 25(21.9)                                    | 24(21.1)                                 | 49(21.5)                          | 0.872           |
| FC NYHA III-IV/IV ( <i>n</i> , %)                                  | 101(88.6)                                   | 97(85.1)                                 | 198(86.8)                         | 0.433           |
| NT-proBNP                                                          | 4821.6 $\pm$ 6364                           | 4715.2 $\pm$ 5715                        | 4762.2 $\pm$ 5990                 | 0.915           |
| EuroScore II                                                       | 8.7 $\pm$ 8.3                               | 8.2 $\pm$ 7.6                            | 8.5 $\pm$ 7.9                     | 0.589           |
| STS-Score                                                          | 5.4 $\pm$ 5.2                               | 6.3 $\pm$ 5.5                            | 5.8 $\pm$ 5.3                     | 0.244           |
| Medical therapy ( <i>n</i> , %):                                   |                                             |                                          |                                   |                 |
| Betablockers                                                       | 86 (76.8)                                   | 90 (78.9)                                | 176 (77.9)                        | 0.695           |
| Mineralocorticoid antagonists                                      | 72 (64.3)                                   | 60 (52.6)                                | 132 (58.4)                        | 0.076           |
| ACE inhibitors/ARB/ARNis                                           | 86 (76.8)                                   | 84 (73.7)                                | 170 (75.2)                        | 0.589           |
| Diuretics                                                          | 108 (96.4)                                  | 109 (95.6)                               | 217 (96)                          | 0.754           |
| <b>Baseline Echocardiographic Characteristics</b>                  |                                             |                                          |                                   |                 |
| LVEDD (mm)                                                         | 60.7 $\pm$ 9.9                              | 61 $\pm$ 10.4                            | 60.9 $\pm$ 10.1                   | 0.838           |
| LVESD (mm)                                                         | 49.9 $\pm$ 12.5                             | 49.9 $\pm$ 12.6                          | 49.9 $\pm$ 12.5                   | 0.975           |
| Indexed LVEDV (mL/m <sup>2</sup> )                                 | 93.4 $\pm$ 34.3                             | 90.9 $\pm$ 34.6                          | 92.1 $\pm$ 34.4                   | 0.623           |
| Indexed LVEDV (mL/m <sup>2</sup> )                                 | 56.6 $\pm$ 31                               | 55.2 $\pm$ 31.3                          | 55.8 $\pm$ 31.1                   | 0.762           |
| LVEF (%)                                                           | 39.3 $\pm$ 14.9                             | 41.4 $\pm$ 15.5                          | 40.4 $\pm$ 15.3                   | 0.283           |
| Indexed LA volume (mL/m <sup>2</sup> )                             | 58.3 $\pm$ 21.2                             | 62.3 $\pm$ 26.8                          | 60.3 $\pm$ 24.2                   | 0.291           |
| MR grade IV/IV ( <i>n</i> , %)                                     | 94(82.5)                                    | 98(86.7)                                 | 187(82.1)                         | 0.373           |
| Regurgitant Volume (mL)                                            | 60 $\pm$ 24.9                               | 58.8 $\pm$ 19.2                          | 59.5 $\pm$ 22.3                   | 0.828           |
| Effective Regurgitant Orifice (mm <sup>2</sup> )                   | 42.6 $\pm$ 16.9                             | 43.6 $\pm$ 18.5                          | 43.1 $\pm$ 17.6                   | 0.741           |
| Indexed LVEDV/ Effective Regurgitant Orifice (mL/mm <sup>2</sup> ) | 2.5 $\pm$ 1.4                               | 2.5 $\pm$ 1.3                            | 2.5 $\pm$ 1.4                     | 0.979           |
| MR aetiology ( <i>n</i> , %) *                                     |                                             |                                          |                                   |                 |
| Primary                                                            | 22(19.3)                                    | 28(25.2)                                 | 50(22.2)                          | 0.439           |
| Secondary                                                          | 79(69.3)                                    | 68(61.3)                                 | 147(65.3)                         |                 |
| Mixed                                                              | 13(11.4)                                    | 15(13.5)                                 | 28(12.4)                          |                 |
| Tricuspid regurgitation ( <i>n</i> , %)                            |                                             |                                          |                                   |                 |
| Grade 0–1                                                          | 35(30.7)                                    | 63(55.3)                                 | 98(43)                            | <0.001          |
| Grade 2                                                            | 29(25.4)                                    | 28(24.6)                                 | 57(25)                            |                 |
| Grade 3                                                            | 29(25.4)                                    | 17(14.9)                                 | 46(20.2)                          |                 |
| Grade 4                                                            | 21(18.4)                                    | 6(5.3)                                   | 27(11.8)                          |                 |
| TAPSE (mm)                                                         | 14.4 $\pm$ 3.3                              | 19.5 $\pm$ 3.7                           | 16.9 $\pm$ 4.3                    | <0.001          |
| PASP (mmHg)                                                        | 57.7 $\pm$ 11.9                             | 40.2 $\pm$ 11.1                          | 48.9 $\pm$ 14.4                   | <0.001          |
| TAPSE/ PASP ratio                                                  | 0.26 $\pm$ 0.1                              | 0.52 $\pm$ 0.16                          | 0.39 $\pm$ 0.18                   | <0.001          |
| <b>Right Heart Catheterization <math>\Phi</math></b>               |                                             |                                          |                                   |                 |
| Right atrial pressure (mmHg)                                       | 9.8 $\pm$ 4.8                               | 8.5 $\pm$ 6.1                            | 9.1 $\pm$ 5.5                     | 0.520           |
| LA mean pressure (mmHg)                                            | 25 $\pm$ 25.5                               | 17.4 $\pm$ 7.6                           | 20.7 $\pm$ 18                     | 0.116           |
| LA V-wave pressure (mmHg)                                          | 42.9 $\pm$ 13.8                             | 29.8 $\pm$ 15.5                          | 36 $\pm$ 15.9                     | 0.010           |

Table 1. Cont.

|                                                      | TAPSE/PASP $\leq 0.35$<br>( <i>n</i> = 114) | TAPSE/PASP $> 0.35$<br>( <i>n</i> = 114) | Total Sample<br>( <i>n</i> = 228) | <i>p</i> -Value |
|------------------------------------------------------|---------------------------------------------|------------------------------------------|-----------------------------------|-----------------|
| <b>Right Heart Catheterization <math>\Phi</math></b> |                                             |                                          |                                   |                 |
| Change in LA mean pressure (mmHg)                    | 6.2 $\pm$ 6.6                               | 5.8 $\pm$ 7.4                            | 5.9 $\pm$ 7.1                     | 0.848           |
| Change in LA v-wave pressure (mmHg)                  | 21.6 $\pm$ 15.7                             | 12.8 $\pm$ 12.9                          | 16.4 $\pm$ 14.6                   | 0.081           |
| PCW pressure (mmHg)                                  | 18.4 $\pm$ 7                                | 19 $\pm$ 7.9                             | 18.7 $\pm$ 7.3                    | 0.833           |
| Mean PA pressure (mmHg)                              | 30.7 $\pm$ 12.4                             | 29.5 $\pm$ 10.9                          | 30.2 $\pm$ 11.5                   | 0.795           |
| Systolic PA pressure (mmHg) $^Y$                     | 52.7 $\pm$ 18.9                             | 41.1 $\pm$ 13.9                          | 47.1 $\pm$ 17.4                   | 0.016           |
| PA Pulse Pressure (mmHg)                             | 28.6 $\pm$ 13.6                             | 23.2 $\pm$ 6.8                           | 26 $\pm$ 11                       | 0.214           |
| Cardiac index (mL/min/m <sup>2</sup> )               | 2.3 $\pm$ 0.6                               | 2.1 $\pm$ 0.6                            | 2.2 $\pm$ 0.6                     | 0.342           |
| Pulmonary vascular resistance (WU)                   | 2.9 $\pm$ 1.5                               | 3.2 $\pm$ 1.2                            | 3.1 $\pm$ 1.3                     | 0.651           |
| Transpulmonary pressure gradient (mmHg)              | 12.6 $\pm$ 7.6                              | 10.8 $\pm$ 3.7                           | 11.8 $\pm$ 6.1                    | 0.442           |
| Diastolic pressure gradient (mmHg)                   | 2.9 $\pm$ 3.7                               | 2.6 $\pm$ 2.5                            | 2.7 $\pm$ 3.2                     | 0.847           |
| PA compliance (mL/mmHg)                              | 2.4 $\pm$ 1.2                               | 2.5 $\pm$ 1.3                            | 2.4 $\pm$ 1.2                     | 0.756           |

\* values for 225 patients.  $\Phi$  values for 26 patients.  $^Y$  values for 51 patients. ACE: angiotensin converting enzyme. ARB: angiotensin receptor blocker. ARNi: Angiotensin receptor neprilysin inhibitors. CABG: coronary artery bypass graft. COPD: chronic obstructive pulmonary disease. LA: left atrial. LVEDD: left ventricular end-diastolic diameter. LVEDV: left ventricular end-diastolic volume. LVEF: left ventricular ejection fraction. LVESD: left ventricular end-systolic diameter. LVESV: left ventricular end-systolic volume. MR: mitral regurgitation. PA: pulmonary artery. PASP: pulmonary artery systolic pressure. PCI: percutaneous coronary intervention. PCW: pulmonary capillary wedge. STS-Score: Society of Thoracic Surgery Score. TAPSE: tricuspid annular plane systolic excursion. WU: wood unit.

Next, the correlation between TAPSE/PASP ratio, a non-invasive index of the RV to PA coupling state and RHC derived variables, including RV to PA coupling parameters, were assessed by means of the Pearson correlation coefficient. TAPSE/PASP presented a positive linear relationship with PA compliance and a negative linear relationship with PA pulse pressure, PASP and LA v-wave pressure, Table 2.

Table 2. Linear correlation analysis between TAPSE/PASP ratio and RHC-derived parameters.

| RHC-Derived Parameters                  | Pearson/Spearman Correlation Coefficients | <i>p</i> -Value |
|-----------------------------------------|-------------------------------------------|-----------------|
| Mean right atrial pressure (mmHg)       | −0.102                                    | 0.606           |
| Mean left atrial pressure (mmHg)        | −0.197                                    | 0.142           |
| Mean left atrial V-wave (mmHg)          | −0.324                                    | 0.047           |
| Mean PCW (mmHg)                         | −0.203                                    | 0.299           |
| Mean PA Pressure (mmHg)                 | −0.236                                    | 0.246           |
| Systolic PA Pressure (mmHg)             | −0.373                                    | 0.007           |
| PA Pulse Pressure (mmHg)                | −0.423                                    | 0.028           |
| Cardiac Index (mL/min/m <sup>2</sup> )  | −0.003                                    | 0.988           |
| Pulmonary vascular resistance (WU)      | −0.103                                    | 0.615           |
| Transpulmonary pressure gradient (mmHg) | −0.168                                    | 0.412           |
| Diastolic pressure gradient (mmHg)      | 0.067                                     | 0.742           |
| PA compliance (mL/mmHg)                 | 0.418                                     | 0.030           |

TAPSE: tricuspid annular plane systolic excursion. PASP: pulmonary artery systolic pressure. PA: Pulmonary artery. PCW: Pulmonary capillary wedge pressure. RHC: right heart catheterization. WU: wood units.

### 3.2. Outcomes

During a median follow-up period of 260 days (IQ range: 115–394), the primary combined endpoint occurred in 71 (31.1%) patients (40.4% TAPSE/PASP  $\leq 0.35$  vs. 21.9% in TAPSE/PASP  $> 0.35$ ,  $p = 0.003$ ), at the expense of 61 (26.8%) HF admissions and 22 (9.6%) all-cause deaths. 12 deaths occurred in patients with a previous hospitalization for HF and

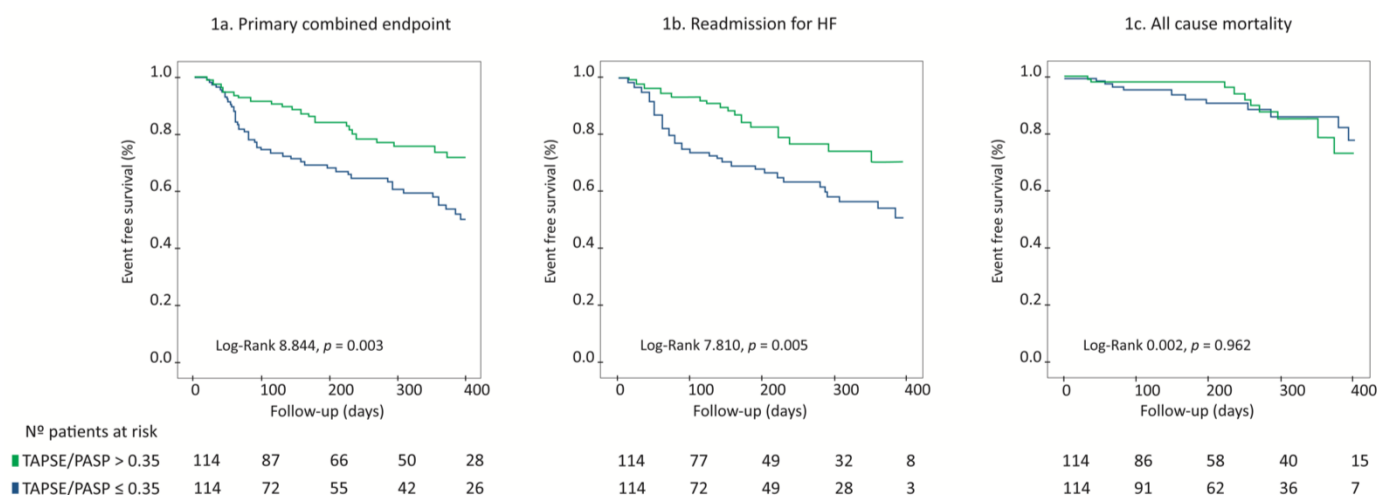
2 during index hospital admission. Cardiovascular mortality accounted for 10 (45.5%) of total deaths.

Higher rates of the primary combined endpoint were noted among patients with diabetes (45.1% vs. 26.8%,  $p = 0.006$ ) and NYHA III to IV functional class at baseline (94.4% vs. 83.4%,  $p = 0.024$ ). STS-Score was numerically higher in patients that met the primary endpoint, although this association was not statistically significant ( $7.1 \pm 6.4$  vs.  $5.3 \pm 4.7$ ,  $p = 0.059$ ), (Table S1). Moreover, the primary combined endpoint occurred more frequently among patients with lower TAPSE and TAPSE/PASP ratio, but there were no significant differences in PASP values. Incidence of device-related and periprocedural complications were low across the whole sample and did not differ according to the primary combined endpoint, with the exception of in-hospital mortality and 30-day readmissions for decompensated HF, (Table S2).

Importantly, a more advanced NYHA III-IV/IV functional class during follow-up was more frequent in patients with reduced TAPSE/PASP at baseline (39.5% vs. 25.7%,  $p = 0.045$ ) and also among patients that maintained a reduced TAPSE/PASP  $\leq 0.35$  after successful TMVR (55.9% vs. 27.8%,  $p = 0.004$ ). Of note, TAPSE/PASP ratio raised over the 0.35 threshold in almost two thirds of patients with baseline TAPSE/PASP  $\leq 0.35$  that had this parameter reassessed after TMVR, (Table S3).

### 3.3. Survival and Multivariate Analysis

On Kaplan–Meier survival analysis, patients with TAPSE/PASP  $\leq 0.35$  had a higher risk of suffering the primary combined endpoint, Log Rank 8.844,  $p = 0.003$ , Figure 1a. When cardiac events were analysed separately, HF readmissions (Log Rank 7.810,  $p = 0.005$ ; Figure 1b) remained significantly more frequent among patients with TAPSE/PASP  $\leq 0.35$ , but there were no differences regarding global mortality according to TAPSE/PASP (Log-Rank 0.002,  $p = 0.962$ ; Figure 1c).



**Figure 1.** Survival analysis according to TAPSE/PASP ratio as shown by Kaplan–Meier curves. TAPSE/PASP ratio  $\leq 0.35$  is associated with higher rates of the primary combined endpoint (a), higher HF readmissions rates (b) without differences in all-cause mortality rates (c). TAPSE: tricuspid annular plane systolic excursion. PASP: pulmonary artery systolic pressure.

In order to assess whether TAPSE/PASP acted as an independent prognostic marker, a Cox proportional hazard analysis was performed, including all baseline and periprocedural characteristics that presented a  $p$ -value  $< 0.10$  on univariate analysis. The ability of the TAPSE/PASP ratio to predict the combined endpoint was assessed against that of TAPSE and PASP to avoid colinearity, and, as only TAPSE/PASP maintained its prognostic significance, TAPSE and PASP were discarded from the final model.

Multivariate Cox regression identified TAPSE/PASP as an independent prognostic marker for the primary combined endpoint (HR 2.0; 95% CI: 1.13–3.53,  $p = 0.017$ ), alongside with STS-Score (HR 1.05; 95% CI: 1.01–1.10,  $p = 0.024$ ), Table 3.

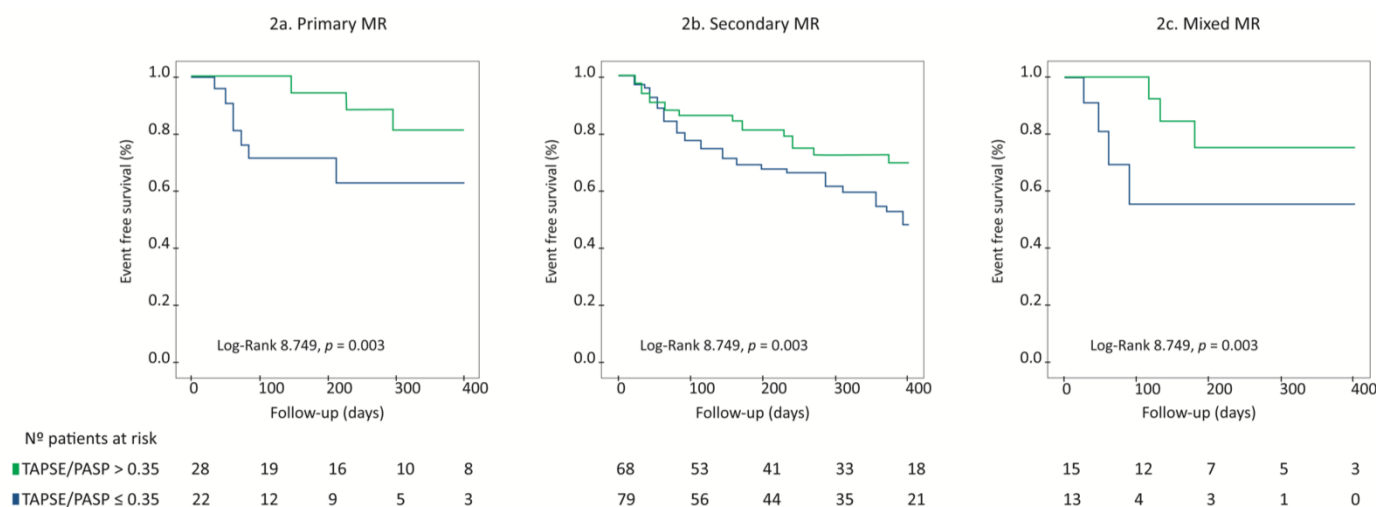


**Table 3.** Multivariate Cox Regression Analysis.

| Variables                             | $\beta$ | Hazard Ratio | 95% CI    | p-Value |
|---------------------------------------|---------|--------------|-----------|---------|
| Diabetes Mellitus                     | 0.442   | 1.56         | 0.92–2.64 | 0.101   |
| NYHA FC III-IV/IV                     | 0.722   | 2.06         | 0.73–5.84 | 0.175   |
| TAPSE/PASP $\leq 0.35$                | 0.693   | 2.0          | 1.13–3.53 | 0.017   |
| STS-Score                             | 0.050   | 1.05         | 1.01–1.10 | 0.024   |
| TR grade III-IV/IV                    | 0.091   | 1.09         | 0.62–1.92 | 0.750   |
| LVEF                                  | −0.003  | 0.99         | 0.98–1.01 | 0.765   |
| <b>Regression Model Tests</b>         |         |              |           |         |
| Concordance = 0.662 (SE = 0.036)      |         |              |           |         |
| Likelihood ratio test                 |         |              |           | 0.001   |
| Wald test                             |         |              |           | 0.002   |
| Score (log rank) test                 |         |              |           | 0.002   |
| <b>Proportional Hazard Assumption</b> |         |              |           |         |
| Diabetes Mellitus                     |         |              |           | 0.54    |
| NYHA FC                               |         |              |           | 0.76    |
| TAPSE/PASP $\leq 0.35$                |         |              |           | 0.93    |
| STS Score                             |         |              |           | 0.96    |
| TR                                    |         |              |           | 0.26    |
| LVEF                                  |         |              |           | 0.54    |
| Global                                |         |              |           | 0.86    |

FC: functional class. NYHA: New-York heart association. LVEF: left ventricular ejection fraction. PASP: pulmonary artery systolic pressure. TAPSE: tricuspid annular plane excursion. TR: tricuspid regurgitation. SE: standard error. STS-Score: Society of Thoracic Surgery Score.

Interestingly, TAPSE/PASP ratio maintained its prognostic value regardless of MR aetiology. On Kaplan–Meier survival analysis, a TAPSE/PASP ratio  $\leq 0.35$  was associated with a higher risk for the primary combined endpoint in patients with primary MR, Figure 2a, secondary MR, Figure 2b, and mixed aetiology MR, Figure 2c, Log Rank 8.749,  $p = 0.003$ . Moreover, when MR aetiology was introduced into Cox Multivariate Regression analysis, TAPSE/PASP  $\leq 0.35$  remained an independent prognostic indicator for the primary combined endpoint (HR: 2.19, 95% CI: 1.18–3.85,  $p = 0.012$ ), together with STS-Score (HR: 1.05, 95% CI: 1.01–1.10,  $p = 0.021$ ).



**Figure 2.** Survival analysis according to TAPSE/PASP ratio as shown by Kaplan–Meier curves, stratified according to MR aetiology. TAPSE/PASP ratio  $\leq 0.35$  is associated with higher rates of the primary combined endpoint in patients with primary MR (a), secondary MR (b) and mixed MR (c).



#### 4. Discussion

To the best of our knowledge, this is the first study to assess the prognostic value of TAPSE/PASP ratio in patients undergoing successful TMVR with the MitraClip system. In this sample, TAPSE/PASP emerged as a prognostic predictor for the primary combined endpoint encompassing HF readmissions and all-cause mortality, alongside with STS-Risk Score. Importantly, TAPSE/PASP ratio provided a better prognostic stratification on multivariate Cox regression analysis than either TAPSE or PASP separately.

RV to PA coupling has recently been established as a valuable prognostic predictor in HF [19–21]. The gold standard for determining RV-PA coupling consists of the ratio between RV end-systolic elastance and effective arterial elastance [Ees/Ea] [17,26], which requires invasive measurements by means of a RHC as well as specific, dedicated material and is thus, rarely employed in clinical practice. Recently, the TAPSE/PASP ratio has been proposed as a non-invasive indicator of RV to PA coupling [19–22,27]. This index provides a valuable non-invasive measure of RV contractile state and RV load adaptability beyond the information afforded by each separate variable as an index of changes in RV length (TAPSE) versus developed force (PASP) [19,21]. Accordingly, TAPSE/PASP ratio may help identify initial stages of RV functional reserve reduction [26], which could account for its improved prognostic accuracy.

Our results are consistent with previous studies that have recently reported the prognostic value of TAPSE/PASP ratio in several HF and PH populations, [19–22], including patients with severe aortic stenosis undergoing transcatheter aortic valve implantation [28]. Indeed, in our sample, TAPSE/PASP ratio displayed a significant linear correlation with PA compliance and PA pulse pressure, both of which are invasive indicators of the distensibility of the pulmonary vascular bed. This observation provides further support on the value of TAPSE/PASP ratio as a non-invasive index of the RV to PA coupling.

In addition, TAPSE/PASP ratio presented a significant negative correlation with baseline LA v-wave pressure. This finding could reflect greater LA stiffness in patients with worse RV to PA coupling as per TAPSE/PASP values, in agreement with prior studies that link loss of LA reservoir function with RV-PA uncoupling [24] and impaired functional class [29,30]. In fact, a reduced TAPSE/PASP ratio  $\leq 0.35$ , either at baseline or after successful TMVR, was associated with worse functional class during follow-up in our study.

Altogether, identification of readily available, accurate prognostic predictors remains especially relevant in patients undergoing MitraClip implantation to avoid futility, as patients considered for this intervention often present advanced HF and a high load of comorbidities. Prior studies have recognized numerous indicators of worse outcomes in this population, including reduced bi-ventricular function, enlarged left ventricular (LV) volumes, PH, severe TR and advanced functional class, amongst others [3,9–15,31].

Our study adds to aforementioned trials as it identifies a novel parameter, the TAPSE/PASP ratio, which improves prognostic stratification of patients undergoing TMVR adding to already known risk indicators, regardless of MR aetiology. This finding is important considering the contradictory results on the utility of MitraClip in patients with HF and secondary MR recently reported by the COAPT and MITRA-FR trials [32,33]. Several parameters such as excessively dilated LV and lower regurgitant volumes have been identified as potential factors that could justify the lack of benefit after MitraClip implantation in the MITRA-FR study [34]. Moreover, inclusion of patients with lower pulmonary pressure and better RV function in COAPT as compared to MITRA-FR trial, which did not exclude patients with severe RV dysfunction and PH, could also account for the diverging results between both trials. In this sense, we believe that assessment of TAPSE/PASP ratio, as a non-invasive index of the RV to PA coupling state, provides clinicians with a useful tool that might improve candidate selection for MitraClip among patients with secondary MR.

In addition, STS-Score, which assembles information on multiple variables with known prognostic relevance, also presented independent prognostic value in our sample,

although weaker than that provided by TAPSE/PASP ratio. Integration of both STS-Score and TAPSE/PASP ratio may improve the assessment of a patients' candidacy for TMVR with MitraClip. Of note, other known prognostic predictors in MitraClip candidates such as LVEF and LV volumes did not improve prognostic stratification in our study, but this should be regarded with caution as LVEF was only mildly reduced and LV volumes mild-to-moderately enlarged across our sample. Similarly, severe TR, which was present in 11.8% of patients, also lacked prognostic value, possible due to lower LV volumes and higher LVEF values observed in these patients.

Notwithstanding, TAPSE/PASP ratio was unable to predict all-cause mortality on a separate basis, which could be due to the relatively low incidence of deaths and their frequent relation to non-cardiovascular causes. Accordingly, further trials with larger samples and follow-up periods that are powered for the detection of hard endpoints, as is mortality, are required to confirm our initial results.

### *Limitations*

Our study has several limitations. First, it is an observational study based on a retrospective analysis of a multicentre registry. Limitations inherent to this design as is the potential existence of confounding factors or selection and follow-up bias cannot be discarded. Moreover, we lacked a central core lab to assess imaging and procedural data and event adjudication were not crosschecked. Accordingly, definite conclusions regarding the clinical value of TAPSE/PASP ratio for the prediction of cardiovascular adverse events cannot be established from this single study and further adequately powered trials will be needed to confirm our initial results. Second, RHC was only conducted in a small subset of the total sample, at the discretion of the patient's physician. This strategy represents real life practice an indeed, a systematic invasive assessment of right chambers pressures via RHC was not performed in the vast majority of studies evaluating prognostic predictors in patients undergoing MitraClip procedure. Thus, a stronger influence of hemodynamic parameters on outcomes cannot be excluded based on our results. Notwithstanding, non-invasive parameters employed in our study such as TAPSE/PASP ratio or echo derived PASP estimation have previously been validated against invasively assessed gold standards [24,26,29] and echo derived PASP displayed a significant correlation with invasively determined PASP in our sample,  $r = 0.592$ ,  $p < 0.0001$ .

### **5. Conclusions**

In this sample of HF patients with significant MR undergoing successful TMVR with MitraClip System, the TAPSE/PASP ratio emerged as a relevant prognostic predictor of the primary combined endpoint encompassing HF readmissions and all-cause mortality, regardless of MR aetiology and TR severity. Importantly, TAPSE/PASP ratio outperformed the prognostic value of each of its components, namely TAPS and PASP, on a separate basis. In agreement with prior investigations, TAPSE/PASP ratio displayed a significant correlation with other parameters evaluating the RV to PA coupling state such as PA compliance and PA pulse pressure, which reinforces its role as a non-invasive indicator of the right-sided cardiopulmonary unit.

**Supplementary Materials:** The following are available online at <https://www.mdpi.com/2077-0383/10/5/1006/s1>, Table S1: Baseline characteristics according to the combined endpoint. Table S2: Procedural and 30-day outcomes according to the combined endpoint. Table S3: Follow-up TAPSE/PASP ratio determinations after successful transcatheter mitral valve repair.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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## 10.8. Anexo 8

Prognostic impact of nutritional status after transcatheter edge-to-edge mitral valve repair: the MIVNUT registry.

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ORIGINAL RESEARCH

# Prognostic Impact of Nutritional Status After Transcatheter Edge-to-Edge Mitral Valve Repair: The MIVNUT Registry

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**BACKGROUND:** Malnutrition is associated with poor prognosis in several cardiovascular diseases. However, its prognostic impact in patients undergoing transcatheter edge-to-edge mitral valve repair (TEER) is not well known. This study sought to assess the prevalence, clinical associations, and prognostic consequences of malnutrition in patients undergoing TEER.

**METHODS AND RESULTS:** A total of 892 patients undergoing TEER from the international MIVNUT (Mitral Valve Repair and Nutritional Status) registry were studied. Malnutrition status was assessed with the Controlling Nutritional Status score. The association of nutritional status with mortality was analyzed with multivariable Cox regression models, whereas the association with heart failure admission was assessed by Fine-Gray models, with death as a competing risk. According to the Controlling Nutritional Status score, 74.4% of patients with TEER had any degree of malnutrition at the time of TEER (75.1% in patients with body mass index  $<25\text{ kg/m}^2$ , 72.1% in those with body mass index  $\geq 25\text{ kg/m}^2$ ). However, only 20% had moderate–severe malnutrition. TEER was successful in most of patients (94.2%). During a median follow-up of 1.6 years (interquartile range, 0.6–3.0), 267 (29.9%) patients died and 256 patients (28.7%) were admitted for heart failure after TEER. Compared with normal nutritional status moderate–severe malnutrition resulted a strong predictor of mortality (adjusted hazard ratio [HR], 2.1 [95% CI, 1.1–2.4];  $P<0.001$ ) and heart failure admission (adjusted subdistribution HR, 1.6 [95% CI, 1.1–2.4];  $P=0.015$ ).

**CONCLUSIONS:** Malnutrition is common among patients submitted to TEER, and moderate–severe malnutrition is strongly associated with increased mortality and heart failure readmission. Assessment of nutritional status in these patients may help to improve risk stratification.

**Key Words:** CONUT ■ heart failure ■ malnutrition ■ mortality ■ transcatheter edge-to-edge repair

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## CLINICAL PERSPECTIVE

### What Is New?

- Most patients undergoing transcatheter edge-to-edge mitral valve repair have malnutrition, even those who are overweight.
- Moderate–severe malnutrition is independently associated with an increased probability of mortality and heart failure admission in patients undergoing transcatheter edge-to-edge mitral valve repair.

### What Are the Clinical Implications?

- Improvement of preprocedural nutritional status may help improve the prognosis of patients undergoing transcatheter edge-to-edge mitral valve repair.

## Nonstandard Abbreviations and Acronyms

|               |                                                |
|---------------|------------------------------------------------|
| <b>CONUT</b>  | Controlling Nutritional Status                 |
| <b>MIVNUT</b> | mitral valve repair and nutritional status     |
| <b>MR</b>     | mitral regurgitation                           |
| <b>TEER</b>   | transcatheter edge-to-edge mitral valve repair |

**T**ranscatheter edge-to-edge mitral valve repair (TEER) has become an alternative to mitral valve surgery in patients with primary mitral regurgitation (MR) deemed at high-risk or inoperable, being the first-line strategy for those patients with secondary MR who remain symptomatic despite guideline-directed medical therapy.<sup>1</sup> However, results are still not homogeneous in all subgroups of patients; baseline, echocardiographic, and procedural characteristics may influence outcomes.<sup>2–5</sup>

Malnutrition is common in patients with heart failure (HF) leading to poor quality of life and increased mortality.<sup>6</sup> Likewise, it has been linked to worse clinical outcomes in patients with acute coronary syndromes,<sup>7</sup> and is getting increasing relevance in patients with valvular heart disease.<sup>8–10</sup>

Nonetheless, no information on nutritional status has been provided for patients referred for TEER. Therefore, we sought to assess the prevalence and prognostic relevance of malnutrition in a cohort of patients referred for TEER.

## METHODS

The data, methods used in the analysis, and materials used to conduct the research are available to any researcher for purposes of reproducing the results or

replicating the procedure, after formal request to the corresponding author.

## Study Population

This study is based on a multicentric international MIVNUT (Percutaneous Mitral Valve Repair and Nutritional Status) registry, which included 1119 patients referred for TEER between 2012 and 2020 from 12 centers in Europe and Canada. Two hundred and twenty-seven patients were excluded by missing data about nutritional status. Final cohort comprised 892 patients. All patients gave informed consent and the local ethics committee approved the protocol.

Patients were classified according to nutritional status by the CONUT (Controlling Nutritional Status) score<sup>11</sup> which assess serum albumin, cholesterol, and total lymphocyte count. A score of 0 to 1 was considered normal; scores of 2 to 4, 5 to 8, and 9 to 12 reflected mild, moderate, and severe malnutrition, respectively. For this study, because of the low number of patients with severe degree of malnutrition (n=13), the moderate and severe categories were merged into a single category (moderate–severe malnutrition).

Body mass index (BMI) was calculated before the procedure for all patients, defined as the body mass (kilograms) divided by the square of the body height (in meters). Patients were classified according to BMI in 2 groups: normal weight (BMI <25 kg/m<sup>2</sup>) and overweight/obesity (BMI ≥25 kg/m<sup>2</sup>).

## Procedure

An interdisciplinary heart team in each institution discussed indication of TEER. The procedure was performed according to standard practices, including fluoroscopic and transesophageal echocardiographic guidance. The number of clips implanted and the selection of the type of device were left to the operators' discretion, as well as medical treatment. Technical success was defined as the successful deployment of at least one clip in the absence of procedural mortality. Acute procedural success was defined as reduction of MR to a grade ≤2+ with a mean transmitral gradient <5 mm Hg.

## End Points

Primary end point was all-cause mortality. Secondary end points were HF readmission and composite event of mortality and HF readmission. Patients were followed up since the procedure date. In the absence of outcomes, time was censored at the last medical contact in primary or secondary care.

## Statistical Analysis

Patients were analyzed separately according to nutritional status. Continuous data were presented as

mean $\pm$ SD and compared using unpaired *t* tests. Categorical data were presented as counts (proportions) and compared using Chi-square tests. The incidence of mortality was estimated using Kaplan–Meier curves. We used Cox proportional hazard regression models to estimate the association of nutritional status with all-cause mortality. For HF admission, death served as a competing risk. Therefore, the incidence of HF admission was estimated using weighted cumulative incidence curves. Furthermore, the association between nutritional status with the hazards and cumulative incidence of HF admission was modeled using Fine-Gray proportional subdistributions hazards model. The proportionality assumption was verified by testing for an interaction between the exposure variable and time, and no relevant violations were found. All analyses were adjusted for age, sex, and all those variables with a statistical association ( $P\leq 0.10$ ) with outcomes in the univariate analysis (see Table S1). To perform parsimonious multivariate models, continuous variables were dichotomized and possible nonlinear associations for the Cox proportional hazards model were tested, without significant interactions were found (Bonferroni-corrected  $P$  value was  $>0.05$ ). Effect estimates from Cox models were reported as hazard ratios (HRs) while those from Fine-Gray models were reported as subdistribution HRs (sHRs) along with 95% CIs. Statistical analyses were conducted using STATA software, version 15 (Stata Corp, College Station, Texas, USA). A 2-sided  $P<0.05$  was considered statistically significant.

## RESULTS

### Malnutrition Prevalence and Baseline Characteristics

According to nutritional status 237 patients (26.6%) had a normal nutritional status, 477 patients (53.4%) had mild malnutrition, and 178 patients (20%) were classified as moderate–severe malnutrition (Figure 1). We found malnutrition in 75.1% of normal weight patients (BMI  $<25$  kg/m<sup>2</sup>) compared with 72.1% throughout overweight/obese patients (BMI  $>25$  kg/m<sup>2</sup>) ( $P=0.312$ ). Baseline characteristics of the study population according to nutritional status are presented in Table.

Rate of functional MR was similar among the 3 nutritional groups (134 patients with normal nutritional status (56.6%), 297 patients with mild malnutrition (62.3%) and 111 patients with moderate–severe malnutrition (62.4%),  $P=0.299$ ). Interestingly, anemia, impaired renal function and poorer functional New York Heart Association class were significantly higher among moderate–severe malnourished patients.

### Procedural Data

Procedural success was achieved in 94.2% of the patients without significant difference between groups: 94.5%, 94.7% and 92.7%, respectively, for normal, mild, and moderate–severe malnutrition ( $P=0.080$ ) and significantly different compared with preprocedure for each nutritional status (Figure 2A). However, the percentage of grade 3–4+ MR was higher as nutritional status worsened (10.5%, 14.1% and 17.5% in patients with normal nutrition, mild malnutrition, and moderate–severe malnutrition, respectively).

### Malnutrition and Outcomes

During a median follow-up of 1.6 years, interquartile range of 0.6–3.0, 267 patients (29.9%) died. Information about the variables associated with all-cause mortality in univariate analysis is shown in Table S1–S11. After adjusting for those variables, age and sex, moderate–severe malnutrition (but not mild) was independently associated with all-cause mortality during follow-up after TEER (HR, 2.07 [95% CI, 1.39–3.07]) (Figure 3A). The complete multivariate analysis is shown in Tables S2 and S3.

During the follow-up, 256 patients (28.7%) were admitted to hospital for HF. After a competing risk analysis, moderate–severe malnutrition emerged as independent predictor of HF admissions (HR, 1.61 [95% CI, 1.09–2.37]) (Figure 3B). Univariate and multivariate analysis for HF admission is shown in Tables S4 through S6.

Moreover, moderate–severe malnutrition was associated with the combined end-point of mortality and HF admission (Figure 3C; Tables S7 and S8).

Despite the differences in patient characteristics between the different hospitals (Table S9), there was no variation in the results of the multivariate analysis after including the different hospitals as a confounding variable.

The analysis of the impact of malnutrition according BMI strata is shown in Tables S10 and S11.

The event rate of the combined end point (mortality and/or HF admission) was higher as the CONUT score increased (HR, 1.07 [95% CI, 1.02–1.13];  $P=0.008$ ) (Figure 4).

Figure 2B shows the functional improvement at 6 months before and after the procedure for each nutritional status. Although functional class at 6 months improved in all 3 nutritional groups it is greater for patients with mild malnutrition (81.5% of patients New York Heart Association I or II) compared with 74% and 67.4% for mild and moderate–severe malnutrition ( $P<0.001$ ).

## DISCUSSION

To our knowledge, this is the first study to assess the impact of malnutrition on TEER outcomes. The main findings of our study can be summarized:



**Figure 1. Population distribution according to nutritional status.**  
BMI indicates body mass index.

1. Most of the patients undergoing TEER have malnutrition, even in those overweight, and 1 out of 5 patients have moderate-severe malnutrition.
2. The risk of mortality and/or HF increases as the nutritional status worsens, making the CONUT score a good predictor of adverse events in this population.

**Table 1. Baseline Characteristics of Percutaneous Mitral Valve Repair Population According to Nutritional Status**

| Variables                          | Malnutrition |            |                 | P value |
|------------------------------------|--------------|------------|-----------------|---------|
|                                    | No           | Mild       | Moderate–Severe |         |
| Age, y                             | 72.3±11.2    | 73.9±10.2  | 74.2±9.0        | 0.081   |
| Female sex, n (%)                  | 96 (40.5)    | 143 (30.0) | 54 (30.3)       | 0.014   |
| Body mass index, kg/m <sup>2</sup> | 26.7±4.9     | 26.2±4.7   | 25.6±4.3        | 0.054   |
| Active smoking, n (%)              | 48 (20.3)    | 109 (22.9) | 30 (16.9)       | 0.233   |
| Arterial hypertension, n (%)       | 157 (66.2)   | 354 (74.2) | 132 (74.2)      | 0.065   |
| Dyslipidemia, n (%)                | 136 (57.4)   | 282 (59.1) | 98 (55.1)       | 0.636   |
| Diabetes, n (%)                    | 62 (26.2)    | 186 (39.0) | 72 (40.4)       | 0.001   |
| Ischemic heart disease, n (%)      | 112 (47.3)   | 274 (57.4) | 115 (65.0)      | 0.001   |
| Peripheral artery disease, n (%)   | 22 (11.5)    | 81 (19.7)  | 37 (22.8)       | 0.013   |
| Prior stroke, n (%)                | 22 (9.3)     | 52 (10.9)  | 20 (11.2)       | 0.758   |
| COPD, n (%)                        | 58 (24.5)    | 101 (21.2) | 33 (18.5)       | 0.334   |
| Atrial fibrillation, n (%)         | 135 (57.0)   | 286 (60.0) | 107 (60.1)      | 0.717   |
| Anemia, n (%)                      | 90 (38.0)    | 262 (54.0) | 134 (75.3)      | <0.001  |
| Creatinine >1.5 mg/dL, n (%)       | 55 (23.2)    | 190 (39.8) | 69 (38.8)       | <0.001  |
| Functional MR, n (%)               | 134 (56.5)   | 297 (62.3) | 111 (62.4)      | 0.299   |
| LVEF ≤40%, n (%)                   | 132 (55.7)   | 290 (60.8) | 116 (65.2)      | 0.142   |
| PAP ≥55 mm Hg, n (%)               | 77 (32.5)    | 135 (28.3) | 61 (34.3)       | 0.258   |
| NYHA class III–IV, n (%)           | 184 (77.6)   | 423 (89.7) | 164 (92.2)      | <0.001  |
| B-blocker, n (%)                   | 189 (79.7)   | 383 (80.3) | 128 (71.9)      | 0.058   |
| ACEI/ARB, n (%)                    | 136 (57.4)   | 261 (54.7) | 79 (44.4)       | 0.022   |
| ARNI, n (%)                        | 22 (9.3)     | 45 (9.4)   | 13 (7.3)        | 0.684   |
| Antialdosteronic, n (%)            | 130 (54.9)   | 232 (48.6) | 87 (48.9)       | 0.268   |
| Diuretic, n (%)                    | 182 (76.8)   | 400 (83.9) | 150 (84.3)      | 0.047   |
| Resynchronization therapy, n (%)   | 33 (13.9)    | 106 (22.2) | 29 (16.3)       | 0.018   |
| ICD, n (%)                         | 58 (24.5)    | 168 (35.2) | 46 (25.8)       | 0.004   |

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitors; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and PAP, pulmonary artery pressure.

### 3. Moderate–severe malnutrition is independently associated with an increased probability of mortality and HF admission

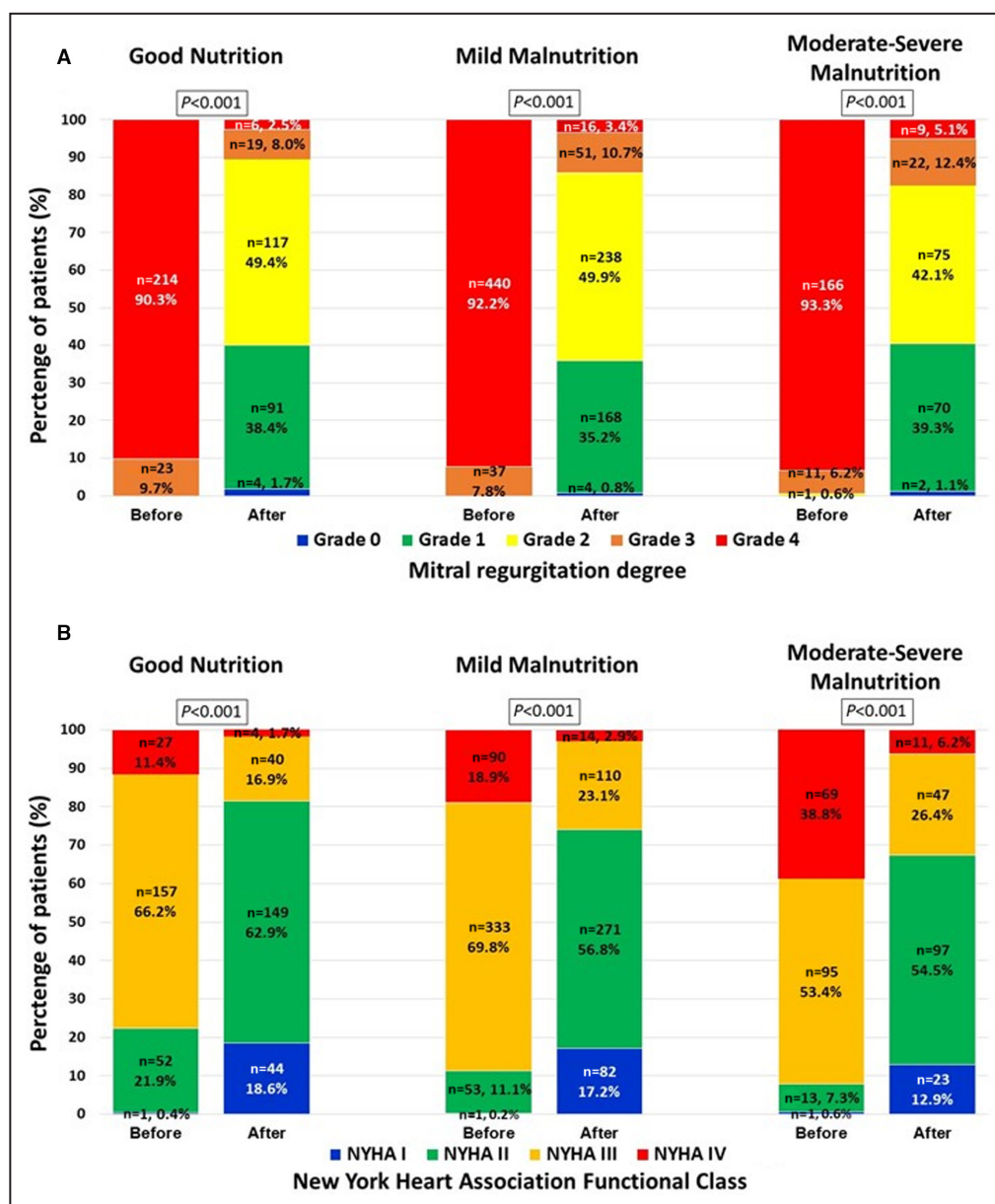
The relevance of malnutrition is given by the fact that is a common finding in patients admitted to hospitals by any cause and it is of special relevance in those linked to the cardiovascular field.<sup>12</sup> In patients undergoing valvular heart surgery it has been reported to be in the range of 10% to 25%<sup>13</sup> and it may increase up to 40% among patients with transcatheter aortic valve replacements.<sup>9</sup> Likewise, in patients with HF any degree of malnutrition is described in 44%.<sup>14</sup> In elderly populations of hospitalized patients this percentage ranges from 30% to 50%.<sup>15</sup> Of interest, in our study this percentage is even higher, around 70%, reflecting probably a more complex profile of patients in which advanced HF, poorer functional class, increased age, frailty, and comorbidities are merging.

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suggest screening for malnutrition in hospitalized patients<sup>16</sup> since patients who are malnourished have more complications, longer length of stay, and greater mortality.<sup>13,17,18</sup> Different screening tools have been compared to assess nutrition risk in patients with HF.<sup>14,19</sup> Nevertheless, simple malnutrition scores not considering anthropometric factors were more related to outcomes than other scores including BMI, not only for patients with HF but also for patients with acute coronary syndrome.<sup>7,14</sup> Taking this into account we selected the CONUT score as the tool for screening malnutrition in our population and simple measures including serum albumin, cholesterol, and lymphocyte count correlated accurately with malnutrition degrees.<sup>11</sup>

It is well recognized that malnutrition has been linked to poor prognosis in the cardiovascular scope.<sup>7–10,20,21</sup> Our population represents a special subset of patients with chronic HF, with a significant proportion of functional patients with MR in advanced functional status, with frequent previous readmissions



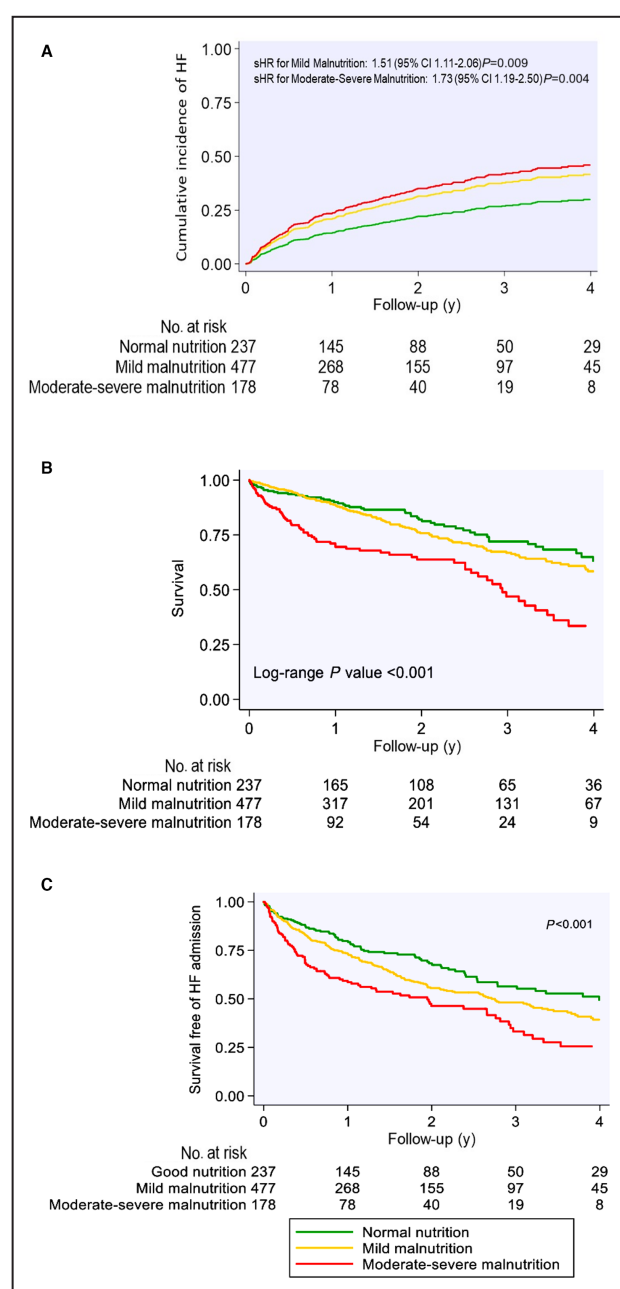


**Figure 2.** Improvement of the mitral regurgitation grade and functional class according to nutritional status.

**A,** Change in mitral regurgitation grade before and after procedure for each nutritional status; **B,** Change in 6-month New York Heart Association functional class for each nutritional group before and after the procedure. NYHA indicates New York Heart Association.

and with symptoms uncontrolled under optimal medical therapy. It is in this type of patient with MR where malnutrition is more frequently found. Advanced HF involves several mechanisms including the presence of chronic inflammation.<sup>22</sup> Inflammation results in acute or chronic-related malnutrition<sup>6</sup> and may be responsible for the wasting syndrome and hypoalbuminemia.<sup>23</sup> It has been also described an improper activation of oxidative processes in patients with chronic HF leading to more tissue damage and more chronic inflammation,

thus creating a vicious circle that might be responsible for an impaired prognosis.<sup>23</sup> Another potentially relevant factor connecting nutrition and adverse prognosis is the link between nutritional status and frailty. Frailty concerns around 46% of patients undergoing TEER<sup>24</sup> and represents a complex syndrome involving physical performance and nutrition.<sup>25</sup> Frailty per se is associated with 3-times increased risk of death and twice the risk of death or HF hospitalization in patients with TEER.<sup>24</sup> As malnutrition is one of the criteria included in



**Figure 3. Primary, secondary, and combined end points according to nutritional status.**

**A**, All-cause mortality; **B**, heart failure readmission; **C**, mortality and heart-failure readmission.

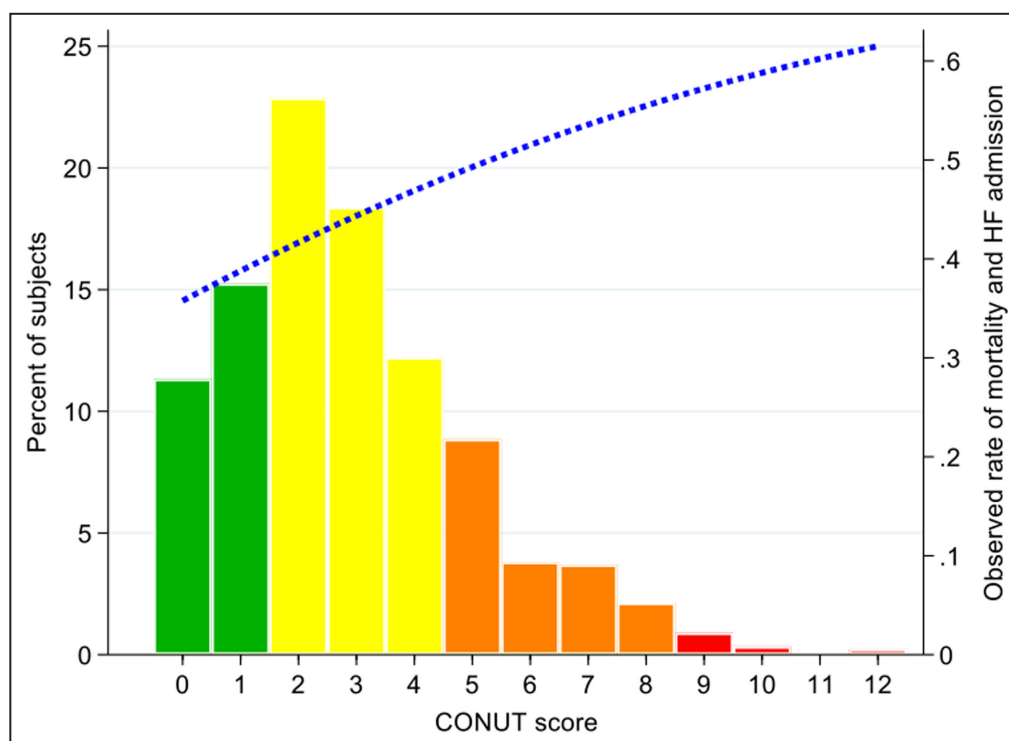
the frailty assessment, we can assume that a proportion of our patients are overlapping those syndromes therefore contributing to the increasing rates of mortality and HF readmission. Thus, we speculate that these features might be responsible for the increased adverse cardiovascular events in patients who are malnourished, irrespective of an adequate MR treatment. On the other hand, it is important to stress that, as it was pointed out by our data and data by Metzger and colleagues,<sup>24</sup> both patients with malnourished and

frailty can be successfully treated by TEER with significant reduction of MR and improvement in New York Heart Association functional class and quality of life. According to nutritional status we can identify patients with greater mortality risk and work to ameliorate it. Therefore, although relevant, malnutrition per se must not be a contraindication for referring patients for percutaneous repair.

The role of assessing malnutrition in our population is relevant because it can be a modifiable factor. It has been reported that nutritional interventions appear to benefit hospitalized patients, by reducing hospital length and readmissions.<sup>26</sup> In addition, there are preliminary data supporting a potential benefit from oral nutritional supplements in patients with HF, with significant reduction in the rate of mortality and hospital readmissions.<sup>27,28</sup> It has been recently reported that those patients who are malnourished undergoing transcatheter aortic valve replacement that improve their nutritional status after the intervention have better prognostic outcomes.<sup>29</sup> This fact may be seen as a signal for a potential target to improve outcomes both in aortic and mitral population, if the nutrition status can be optimized beforehand. Unfortunately, we did not assess nutritional status change after mitral repair, and this hypothesis is speculative. However, given the potential benefit of such strategy we should consider future trials based on nutritional interventions for optimizing TEER outcomes.

## Study Limitations

This is a multicenter retrospective investigation with the subsequent disadvantages secondary to its nature. In addition to this, data about nutritional status were available in 892 from 1119 patients (79.7%). This fact could be a source of selection bias. The rest of data for all analyzed variables were available in all patients. Since malnutrition is a complex issue, especially in older adults, because of diversity in cause and a wide range of determinants, a more complex comprehensive nutritional assessment would be recommendable. We did not evaluate the association of malnutrition scores with inflammatory markers, nor with body composition. However, CONUT score is easy to calculate and to implement as part of routine in clinical practice and does not require specific anthropometric measurements or subjective questionnaires. In this sense, operators can be more prone to use this tool because of the aforementioned advantages. Moreover, given that the nutritional evaluation was conducted only in a single time point, we did not investigate the changes in nutritional status over time and their relationship with cardiovascular outcomes. Information about frailty status and its correlation with malnutrition would be interesting; however, unfortunately, data about frailty were not available



**Figure 4. Rate of mortality and heart failure admission according to Controlling Nutritional Status score.**

CONUT indicates Controlling Nutritional Status; and HF, heart failure.

in the MIVNUT database. Moreover, we have no data about infective endocarditis during the follow-up. And regarding medical therapy, we only had data about treatment at discharge. Confirmation of our findings by other investigators and other countries with different health care and social systems would be welcome.

## ARTICLE INFORMATION

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None.

### Disclosures

Dr Freixa is a consultant for Abbott Vascular. Dr Arzamendi is a consultant for Abbott Vascular and Edwards Lifesciences. Drs Nombela-Franco and De Agustin have served as proctors for Abbott. Dr Rodés-Cabau holds the Canadian Research Chair "Fondation Famille Jacques Larivière" for the development of structural heart disease. Dr Estevez-Loureiro is consultant for Abbott Vascular, Boston Scientific, and Edwards Lifesciences. The remaining authors have no disclosures to report.

### Supplemental Material

Tables S1–S11

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## 10.9. Anexo 9

A score to assess mortality after percutaneous mitral valve repair.

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# A Score to Assess Mortality After Percutaneous Mitral Valve Repair



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## ABSTRACT

**BACKGROUND** Risk stratification for transcatheter edge-to-edge mitral valve repair (TEER) is paramount in the decision-making process for treating severe mitral regurgitation (MR).

**OBJECTIVES** This study sought to create and validate a user-friendly score (MitraScore) to predict the risk of mortality in patients undergoing TEER.

**METHODS** The derivation cohort was based on a multicentric international registry that included 1,119 patients referred for TEER between 2012 and 2020. Score discrimination was assessed using Harrell's c-statistic, and the calibration was evaluated with the Gronnesby and Borgan goodness-of-fit test. An external validation was carried out in 725 patients from the GIOTTO registry.

**RESULTS** After multivariate analysis, we identified 8 independent predictors of mortality during the follow-up ( $2.1 \pm 1.8$  years): age  $\geq 75$  years, anemia, glomerular filtrate rate  $< 60$  mL/min/1.73 m<sup>2</sup>, left ventricular ejection fraction  $< 40\%$ , peripheral artery disease, chronic obstructive pulmonary disease, high diuretic dose, and no therapy with renin-angiotensin system inhibitors. The MitraScore was derived by assigning 1 point to each independent predictor. The c-statistic was 0.70. Per each point of the MitraScore, the relative risk of mortality increased by 55% (HR: 1.55; 95% CI: 1.44-1.67;  $P < 0.001$ ). The discrimination and calibration for mortality prediction was better than those of EuroSCORE II (c-statistic 0.61) or Society of Thoracic Surgeons score (c-statistic 0.57). The MitraScore maintained adequate performance in the validation cohort (c-statistic 0.66). The score was also predictive for heart failure rehospitalization and was correlated with the probability of clinical improvement.

**CONCLUSIONS** The MitraScore is a simple prediction algorithm for the prediction of follow-up mortality in patients treated with TEER. (J Am Coll Cardiol 2022;79:562-573) © 2022 by the American College of Cardiology Foundation.



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**M**itral regurgitation (MR), one of the most common valve diseases, affects approximately 5 in 10,000 people.<sup>1</sup> More than 4 million people have significant MR in the United States.<sup>2</sup> In Europe, nearly 10% of people aged  $\geq 75$  years have moderate or severe MR.<sup>3</sup> If left untreated, patients with symptomatic MR have a poor prognosis, even with optimal medical therapy, progressing to heart failure (HF) and eventually death.<sup>4</sup> However, approximately 50% of symptomatic patients with severe MR are not candidates for surgery due to underlying factors.<sup>5,6</sup>

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Although transcatheter edge-to-edge mitral valve repair (TEER) with MitraClip (Abbott Vascular) began as an alternative to surgery in high surgical-risk patients, as a result of large-scale clinical experience,<sup>7-11</sup> TEER has become the first-line interventional treatment option for secondary MR, and second-line therapy for primary MR with high surgical risk.<sup>12</sup>

A lesson derived from the 2 most recent randomized trials on secondary MR<sup>7,11</sup> showed us that still a significant proportion of patients in the intervention arm presented clinical events. Thus, a better characterization and stratification of this population may allow distinction between those patients who may obtain clinical benefit and those whose procedure may be futile. Nonetheless, risk stratification for TEER is scarcely studied.<sup>12,13</sup> Scores derived from surgical patients predicting perioperative mortality, such as EuroSCORE II and Society of Thoracic Surgeons (STS) score, showed weak stratification capability in the TEER population.<sup>14</sup> Likewise, specific HF scores, such as the Get With the Guidelines Heart Failure Risk Score,<sup>15</sup> provide suboptimal performance. Therefore, the aim of this study was to create and validate a user-friendly score (MitraScore) to predict the risk of mortality in patients undergoing TEER.

## METHODS

**STUDY POPULATION.** This study is based on the multicentric international MIVNUT registry (Percutaneous Mitral Valve Repair and Nutritional Status Registry). The MIVNUT Registry is a retrospective registry of patients with symptomatic MR who underwent TEER in Europe and Canada. A total of 1,119 patients referred for TEER between 2012 and 2020

from 12 centers in Europe and Canada were included. Follow-up and vital status data were not available in 10 patients, who were excluded from the analysis. Therefore, the final cohort comprised 1,109 patients. This study conforms to the principles of the Declaration of Helsinki, and all patients gave their consent for inclusion. The local ethics committees approved the protocol.

**PROCEDURE.** An interdisciplinary heart team in each institution discussed the indication of TEER. The procedure was carried out according to standard practices, including fluoroscopic and transesophageal echocardiographic guidance. The number of clips implanted and the selection of the type of device were left to the operators' discretion, as well as medical treatment.

**FOLLOW-UP AND ENDPOINTS.** Patients were followed-up from the procedure date up to November 2020. Physicians independently reviewed the clinical history of each patient to identify events. The primary endpoint was all-cause mortality. Secondary endpoints were the composite endpoint of mortality and HF readmission, cardiovascular (CV) mortality, and 1-year improvement in New York Heart Association (NYHA) functional class. CV death included mortality resulting from acute myocardial infarction (AMI), sudden cardiac death, death due to HF, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes.<sup>16</sup> HF hospitalization was defined according to the universal definition of HF.<sup>17</sup> Data on vital status and information about HF readmission and NYHA functional class were obtained from hospital and/or administrative data records (vital statistics records, hospital discharge data, and emergency department data), by contacting the patients or their relatives by phone, and/or by contacting the primary care physicians for additional information, when necessary. In the absence of outcomes, time was censored at the last medical contact.

**STATISTICAL ANALYSIS.** Continuous data were presented as mean  $\pm$  SD and compared using unpaired Student's *t*-tests. Categorical data were presented as counts (proportions) and compared using chi-square tests. The rate of cumulative events at follow-up was calculated using the Kaplan-Meier method. The

## ABBREVIATIONS AND ACRONYMS

**CV** = cardiovascular

**HF** = heart failure

**MR** = mitral regurgitation

**RAS** = renin angiotensin system

**STS** = Society of Thoracic Surgeons

**TEER** = transcatheter edge-to-edge mitral valve repair

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**TABLE 1** Univariate and Multivariate Analysis for Mortality Risk Prediction

|                                           | Univariate |           |         | Multivariate |           |         |
|-------------------------------------------|------------|-----------|---------|--------------|-----------|---------|
|                                           | HR         | 95% CI    | P Value | HR           | 95% CI    | P Value |
| Age ≥75 y                                 | 1.48       | 1.19-1.82 | <0.001  | 1.46         | 1.16-1.83 | <0.001  |
| Female                                    | 0.77       | 0.61-0.96 | 0.022   | 0.89         | 0.70-1.13 | 0.338   |
| Body mass index, per kg/m <sup>2</sup>    | 0.98       | 0.96-1.01 | 0.982   | —            | —         | —       |
| Moderate-severe malnutrition              | 1.29       | 1.04-1.60 | 0.018   | 0.99         | 0.80-1.24 | 0.983   |
| Active smoking                            | 0.82       | 0.64-1.04 | 0.109   | —            | —         | —       |
| Diabetes                                  | 1.45       | 1.17-1.79 | 0.001   | 1.08         | 0.86-1.36 | 0.491   |
| Hypertension                              | 1.11       | 0.88-1.42 | 0.375   | —            | —         | —       |
| Dyslipidemia                              | 1.02       | 0.82-1.26 | 0.867   | —            | —         | —       |
| Ischemic heart disease                    | 1.33       | 1.07-1.65 | 0.009   | 1.15         | 0.91-1.45 | 0.234   |
| Peripheral artery disease                 | 1.70       | 1.33-2.17 | <0.001  | 1.34         | 1.03-1.72 | 0.026   |
| Prior stroke                              | 1.07       | 0.76-1.49 | 0.705   | —            | —         | —       |
| Atrial fibrillation                       | 1.17       | 0.94-1.45 | 0.155   | —            | —         | —       |
| NYHA functional class III/IV              | 1.69       | 1.19-2.41 | 0.004   | 1.12         | 0.77-1.62 | 0.546   |
| Prior HF admission                        | 1.61       | 1.26-2.06 | <0.001  | 1.25         | 0.96-1.62 | 0.097   |
| COPD                                      | 1.46       | 1.16-1.84 | 0.001   | 1.51         | 1.19-1.91 | 0.001   |
| Previous TAVR                             | 1.62       | 0.95-2.77 | 0.078   | 1.19         | 0.69-2.05 | 0.533   |
| Anemia                                    | 1.86       | 1.49-2.32 | <0.001  | 1.52         | 1.20-1.93 | <0.001  |
| Thrombopenia (<100 × 10 <sup>3</sup> /μL) | 0.95       | 0.54-1.69 | 0.869   | —            | —         | —       |
| CKD-EPI <60 mL/min/1.73 m <sup>2</sup>    | 1.90       | 1.49-2.44 | <0.001  | 1.65         | 1.28-2.14 | <0.001  |
| Functional MR                             | 0.96       | 0.77-1.19 | 0.700   | —            | —         | —       |
| LVEF ≤40%                                 | 1.30       | 1.04-1.62 | 0.020   | 1.42         | 1.11-1.81 | 0.005   |
| LVEDD, per mm                             | 1.00       | 0.99-1.01 | 0.610   | —            | —         | —       |
| LVEDV, per mL                             | 1.00       | 0.99-1.00 | 0.825   | —            | —         | —       |
| LA volume, per mL                         | 0.99       | 0.99-1.00 | 0.502   | —            | —         | —       |
| Moderate-severe TR                        | 1.29       | 1.02-1.63 | 0.031   | 1.20         | 0.94-1.53 | 0.142   |
| TAPSE <18 mm                              | 0.96       | 0.76-1.21 | 0.730   | —            | —         | —       |
| PASP >50 mm Hg                            | 1.17       | 0.95-1.45 | 0.137   | —            | —         | —       |
| Oral anticoagulation                      | 1.02       | 0.82-1.25 | 0.884   | —            | —         | —       |
| Beta-blocker                              | 0.90       | 0.70-1.15 | 0.410   | —            | —         | —       |
| RAS inhibitor (negative)                  | 1.82       | 1.47-2.24 | <0.001  | 1.55         | 1.24-1.93 | <0.001  |
| Spironolactone                            | 0.99       | 0.80-1.22 | 0.927   | —            | —         | —       |
| High diuretic dose                        | 1.60       | 1.29-1.98 | <0.001  | 1.44         | 1.15-1.81 | 0.002   |
| Hemodynamic instability                   | 1.42       | 1.12-1.81 | 0.003   | 1.08         | 0.84-1.39 | 0.551   |
| Unsuccessful procedure                    | 1.76       | 1.15-2.68 | 0.009   | 1.53         | 0.99-2.36 | 0.052   |

COPD = chronic obstructive pulmonary disease; HF = heart failure; LA = left atria; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; RAS = renin angiotensin system; TAVR = transcatheter aortic valve replacement; TR = tricuspid regurgitation.

study complied with the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement. Independent predictors of follow-up mortality among clinical and echocardiographic preprocedural candidate variables were identified using a multivariable Cox proportional hazard regression model. The proportional hazard assumption was verified with the Schoenfeld residuals and by visual inspection of the log-(minus log) curves. The linearity assumption was tested by plotting the martingale residuals against continuous covariates. Univariate and multivariate Cox proportional hazard regression models are presented with results reported as HR and 95% CI. For all

analyses, a *P* value <0.05 was considered to be statistically significant. Analyses were performed using SPSS Statistics 25 (IBM), Stata/SE 15.1 (StataCorp LP), and R version 3.6.3 software (R Foundation for Statistical Computing).

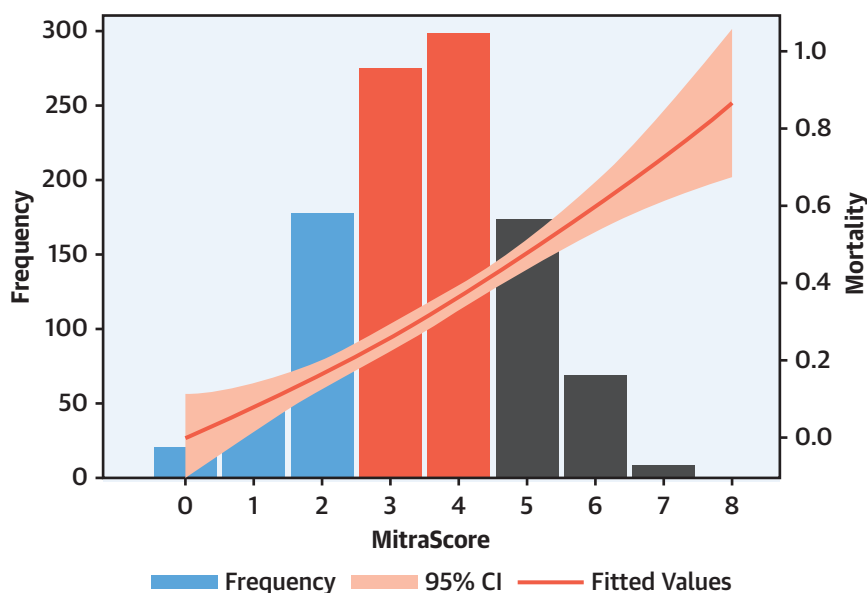
**RISK SCORE DERIVATION.** A total of 17 baseline characteristics arranged in a dichotomous fashion were entered in the conventional multivariate model by univariate preselection with a *P* value <0.10. Those variables that were significant (*P* < 0.05) in the multivariate stepwise (backward elimination) analysis were retained in the final model and were used to develop the MitraScore. Given that the HRs of all of them was similar (between 1.3 and 1.6), we decided to construct the score by a simple arithmetic sum of the number of risk variables (which it is also equivalent to assign 1 point to each variable) to make a simple and user-friendly score. Patients were classified into 3 risk groups of MitraScore by tertiles: low-risk (≤25th percentile), moderate-risk (25-75th percentile), and high-risk (≥75th percentile).

**MISSING DATA.** There was <10% of missing baseline data in the analyzed variables of the MIVNUT registry. As we have a low percentage of missing values that allow us to do single imputation, missing data were singly imputed and replaced with sex-specific medians for continuous variables and to the lower-risk group for categorical variables, to develop our score.

**PERFORMANCE OF MitraScore AND EXTERNAL VALIDATION.** Score discrimination was assessed using Harrell's c-statistic (with values ranging from 0.5 for no discrimination to 1.0 for perfect discrimination). The calibration of the score's performance was investigated by plotting the predicted and observed probabilities of events across increasing levels of predicted risk, and was evaluated using a goodness-of-fit test proposed by Gronnesby and Borgan for Cox proportional hazard models. To compare the predictive ability of the MitraScore with EuroSCORE II and STS score, continuous net reclassification improvement and integrated discrimination improvement were calculated. An external validation was performed using data from the GIOTTO (Italian Society of Interventional Cardiology [GISE] Registry Of Transcatheter Treatment of Mitral Valve Regurgitation). The GIOTTO registry is an ongoing single-arm, multicenter, prospective registry of patients with symptomatic MR who underwent TEER with MitraClip in Italy. This registry was conceived to collect data from MitraClip procedures reflecting standard clinical practice in Italian hospitals linked to the GISE network, analyzing effects on survival,

# **CENTRAL ILLUSTRATION** The MitraScore to Predict Mortality After Transcatheter Mitral Valve Repair

| MitraScore                          |         |
|-------------------------------------|---------|
| Variable                            | Points  |
| ≥75 years of age                    | 1 point |
| LVEF <40%                           | 1 point |
| Anemia                              | 1 point |
| eGFR <60 mL/min/1.73 m <sup>2</sup> | 1 point |
| Peripheral artery disease           | 1 point |
| COPD                                | 1 point |
| High dose of diuretic               | 1 point |
| No therapy with RAS inhibitors      | 1 point |



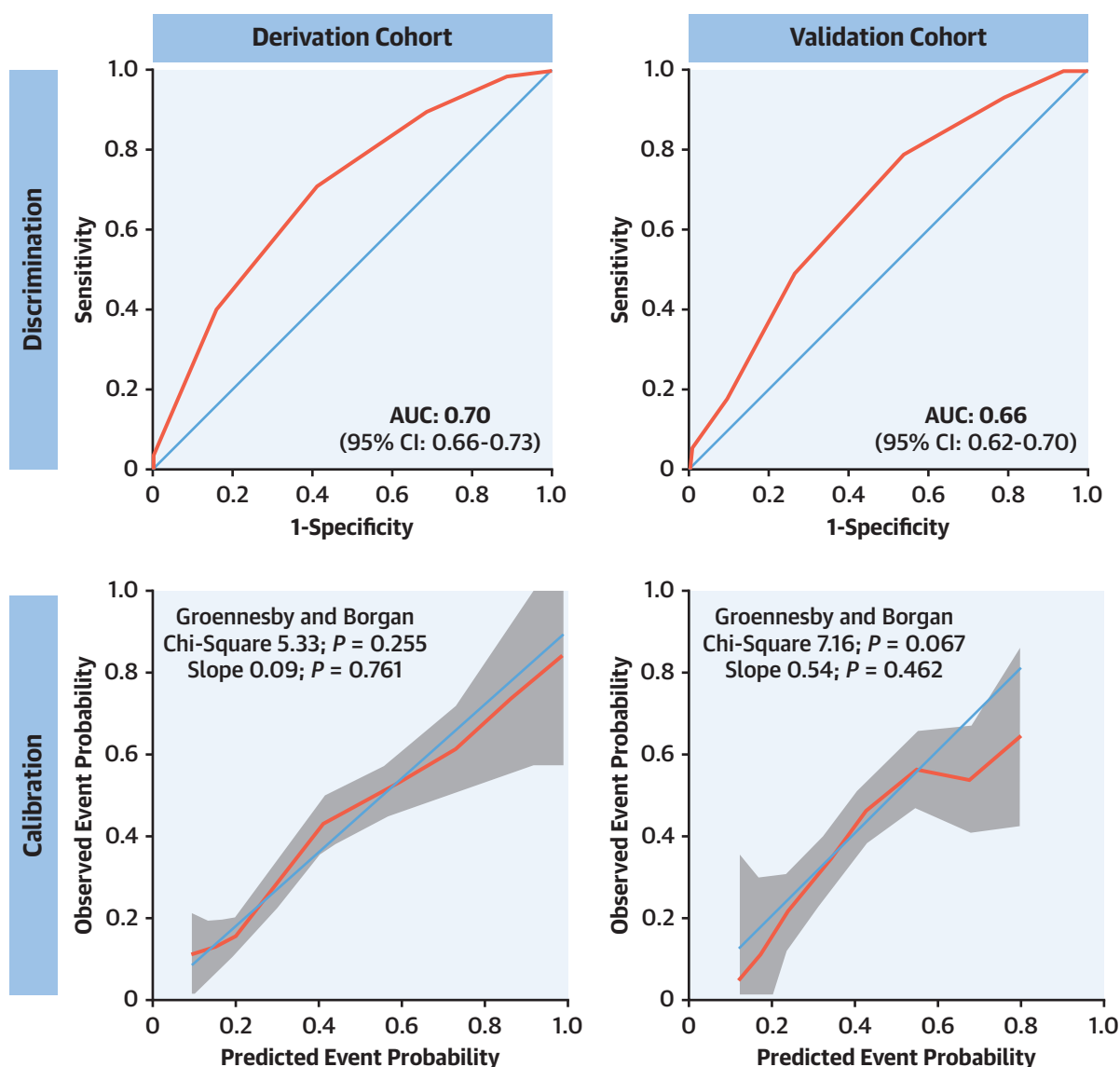
Raposeiras-Roubin, S. *et al.* J Am Coll Cardiol. 2022;79(6):562-573.

The MitraScore is composed of 8 clinical variables each scored with 1 point. It is a simple algorithm that can be easily ascertained before a patient with MR is evaluated for transcatheter mitral valve repair to assess the risk of follow-up mortality. The predicted incidence of mortality, estimated using a quadratic fit, is shown by the **red line** with its 95% CI, and it is represented in the right y-axis. COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; RAS = renin angiotensin system.

hospitalization and quality of life up to 5 years. Data from 1,659 consecutive procedures performed since 2016 and entered in the GIOTTO registry were analyzed. A web-based electronic case report form, periodically crosschecked for accuracy, was used for data collection. Subsequent follow-up data were obtained by inpatient or outpatient clinical visits and/or

telephone calls scheduled at 30 days, 1 year, and yearly thereafter. Qualifying inclusion and exclusion criteria, echocardiographic selection and protocols employed, as well as details of the MitraClip procedure have been reported previously.<sup>18,19</sup> From the initial cohort of 1,659 patients undergoing TEER between 2016 and 2020 in 22 centers from Italy, we have



**FIGURE 1** Discrimination and Calibration of MitraScore in Derivation and Validation Cohorts

Discrimination was assessed using Harrell's c-statistic (with values ranging from 0.5 for no discrimination to 1.0 for perfect discrimination). The calibration of the score's performance was investigated by plotting the predicted and observed probabilities of events across increasing levels of predicted risk, and was evaluated using a goodness-of-fit test proposed by Gronnesby and Borgan for Cox proportional hazard models. AUC = area under the curve.

selected those patients with data about MitraScore variables ( $n = 725$ ). The MitraScore was calculated and assigned to each participant in a similar manner as in the derivation cohort

**NYHA FUNCTIONAL CLASS SUBANALYSIS.** A sub-analysis about the impact of MitraScore risk groups in different NYHA functional classes at 1 year was performed in both cohorts. However, data of 1-year

NYHA functional class were only available in 733 (66.1%) and 525 (72.4%) patients, in derivation and validation cohorts, respectively.

## RESULTS

**MORTALITY INCIDENCE AND PREDICTORS.** Baseline characteristics of MIVNUT registry population are

**TABLE 2** Performance of the MitraScore to Predict Outcomes According to the Etiology of MR

| Event and Group | Derivation Cohort |           |                 |         | Validation Cohort |           |                 |         |
|-----------------|-------------------|-----------|-----------------|---------|-------------------|-----------|-----------------|---------|
|                 | Discrimination    |           | Goodness-of-Fit |         | Discrimination    |           | Goodness-of-Fit |         |
|                 | AUC               | 95% CI    | Chi-Square      | P Value | AUC               | 95% CI    | Chi-Square      | P Value |
| Death           |                   |           |                 |         |                   |           |                 |         |
| All MR          | 0.70              | 0.66-0.73 | 5.33            | 0.255   | 0.66              | 0.62-0.70 | 7.16            | 0.067   |
| Degenerative MR | 0.71              | 0.66-0.76 | 2.92            | 0.233   | 0.67              | 0.60-0.75 | 0.03            | 0.858   |
| Functional MR   | 0.69              | 0.64-0.73 | 6.05            | 0.195   | 0.65              | 0.60-0.70 | 4.21            | 0.240   |
| CV death        |                   |           |                 |         |                   |           |                 |         |
| All MR          | 0.66              | 0.62-0.70 | 3.44            | 0.179   | 0.65              | 0.60-0.71 | 0.76            | 0.385   |
| Degenerative MR | 0.67              | 0.61-0.74 | 2.80            | 0.094   | 0.69              | 0.58-0.79 | 0.97            | 0.324   |
| Functional MR   | 0.66              | 0.61-0.70 | 0.94            | 0.626   | 0.63              | 0.57-0.69 | 0.35            | 0.555   |
| Death and HF    |                   |           |                 |         |                   |           |                 |         |
| All MR          | 0.67              | 0.63-0.70 | 2.79            | 0.593   | 0.65              | 0.61-0.69 | 6.68            | 0.154   |
| Degenerative MR | 0.68              | 0.63-0.73 | 2.62            | 0.455   | 0.63              | 0.56-0.71 | 0.01            | 0.934   |
| Functional MR   | 0.65              | 0.61-0.70 | 2.63            | 0.622   | 0.65              | 0.60-0.70 | 7.50            | 0.058   |

Abbreviations as in Table 1.

summarized in Supplemental Table 1. During a median follow-up of 1.6 years (IQR: 0.7-3.1 years), 354 died (31.9%) and 315 (28.4%) were readmitted by HF. The incidence rate of mortality was 15.3 per 100 person-years (95% CI: 13.8-16.9 per 100 person-years), and 55.6% of deaths were CV (n = 197). After univariate and multivariate analysis (Table 1), we identified 8 independent predictors of mortality: age  $\geq 75$  years, anemia, estimated glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup>, left ventricular ejection fraction  $< 40\%$ , peripheral artery disease, chronic obstructive pulmonary disease, high diuretic dose ( $\geq 80$  mg of furosemide/d or use of  $\geq 2$  diuretic agents excluding antialdosteronic drugs), and no therapy with renin-angiotensin system (RAS) inhibitors. The c-statistic for the multivariate model was 0.70 (95% CI: 0.67-0.73).

**MitraScore PREDICTIVE ACCURACY.** The MitraScore was derived by assigning 1 point to each independent predictor, as is shown in the Central Illustration. The sum of the weighted integers (range 0 to 8 points) estimates the risk of follow-up mortality. Per each point of the MitraScore, the relative risk of mortality increased by 55% (HR: 1.55; 95% CI: 1.44-1.67;  $P < 0.001$ ). There was a curvilinear relationship between the MitraScore and the predicted probabilities of mortality (Figure 1), with an overall 20-fold increase in the mortality rate ( $< 3\%$ - $> 60\%$ ) from the lowest to the highest scores. The risk score exhibited adequate performance in the derivation cohort (c-statistic: 0.70, 95% CI: 0.66-0.73), without differences according to the etiology of MR (Table 2). Calibration was also good (Figure 1). The discrimination and calibration of MitraScore for mortality

prediction was better than those of EuroSCORE II or STS score (Table 3, Supplemental Table 2, and Supplemental Figure 1). A monotonic increase in the risk of mortality (Figure 2) and death and/or HF hospitalization (Figure 3) from the lower to the higher-risk category was observed through the established MitraScore risk groups. A simplified MitraScore was as well calculated without data regarding medical therapy. However, its discriminative capacity was notably diminished (see Supplemental Table 3). Procedural success, defined according to the Mitral Valve Academic Research Consortium, was achieved in most patients (94.8%). Unsuccessful TEER procedure was associated with higher mortality rates in the univariate analysis (HR: 1.76; 95% CI: 1.15-2.68;  $P = 0.009$ ), and showed a trend in the multivariate analysis (HR: 1.53; 95% CI: 0.99-2.36;  $P = 0.052$ ). After adding unsuccessful TEER procedure to MitraScore, the c-statistic of the model was similar in the derivation cohort (0.69; 95% CI: 0.66-0.73).

**EXTERNAL VALIDATION.** The MitraScore maintained adequate discrimination and calibration in the validation cohort (AUC: 0.66; 95% CI: 0.62-0.70). The predictive accuracy for mortality, CV death, and mortality and/or HF was good in both degenerative and functional MR (Table 2), showing a predictive performance improvement in comparison with EuroSCORE II or STS score (Table 3). The 3 MitraScore risk groups adequately stratified the risk of death and/or hospitalization for HF (Figure 3). After adding unsuccessful TEER procedure to MitraScore, the c-statistic of the model in the validation cohort was also similar (0.68; 95% CI: 0.64-0.72).

**TABLE 3** Comparison of Predictive Abilities of MitraScore, EuroSCORE II, and STS Score for All-Cause Mortality

| Mortality Discrimination and Calibration                                                                                             |                            | MitraScore       | EuroSCORE II            | STS Score |
|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------|------------------|-------------------------|-----------|
| Derivation                                                                                                                           |                            |                  |                         |           |
| c-statistic (95% CI)                                                                                                                 | 0.70 (0.66-0.73)           | 0.61 (0.57-0.64) | 0.57 (0.53-0.61)        |           |
| Grønnesby and Borgan test                                                                                                            |                            |                  |                         |           |
| Chi-square                                                                                                                           | 5.33                       | 26.04            | 16.35                   |           |
| P Value                                                                                                                              | 0.255                      | <0.001           | 0.012                   |           |
| Validation                                                                                                                           |                            |                  |                         |           |
| c-statistic (95% CI)                                                                                                                 | 0.66 (0.62-0.70)           | 0.61 (0.57-0.65) | 0.64 (0.58-0.70)        |           |
| Grønnesby and Borgan test                                                                                                            |                            |                  |                         |           |
| Chi-square                                                                                                                           | 7.16                       | 6.57             | 6.25                    |           |
| P Value                                                                                                                              | 0.067                      | 0.161            | 0.013                   |           |
| Comparison of Risk Scores                                                                                                            | MitraScore vs EuroSCORE II |                  | MitraScore vs STS Score |           |
|                                                                                                                                      | Difference                 | P Value          | Difference              | P Value   |
| Derivation                                                                                                                           |                            |                  |                         |           |
| c-statistic                                                                                                                          | 0.09                       | 0.005            | 0.13                    | <0.001    |
| cNRI                                                                                                                                 | 0.254                      | <0.001           | 0.210                   | <0.001    |
| IDI                                                                                                                                  | 0.079                      | <0.001           | 0.065                   | <0.001    |
| Validation                                                                                                                           |                            |                  |                         |           |
| c-statistic                                                                                                                          | 0.05                       | 0.185            | 0.02                    | 0.314     |
| cNRI                                                                                                                                 | 0.248                      | 0.020            | 0.046                   | 0.030     |
| IDI                                                                                                                                  | 0.052                      | 0.030            | 0.171                   | 0.070     |
| cNRI = continuous net reclassification improvement; IDI = integrated discrimination improvement; STS = Society of Thoracic Surgeons. |                            |                  |                         |           |

**IMPROVEMENT IN NYHA FUNCTIONAL CLASS.** The MitraScore identified as well those patients with a better response in terms of functional class, both in the derivation and validation cohorts (Figure 4). Although low-risk MitraScore patients were more frequently in NYHA functional class I-II after TEER, high-risk MitraScore patients showed also a significant improvement in NYHA functional class (Figure 4).

## DISCUSSION

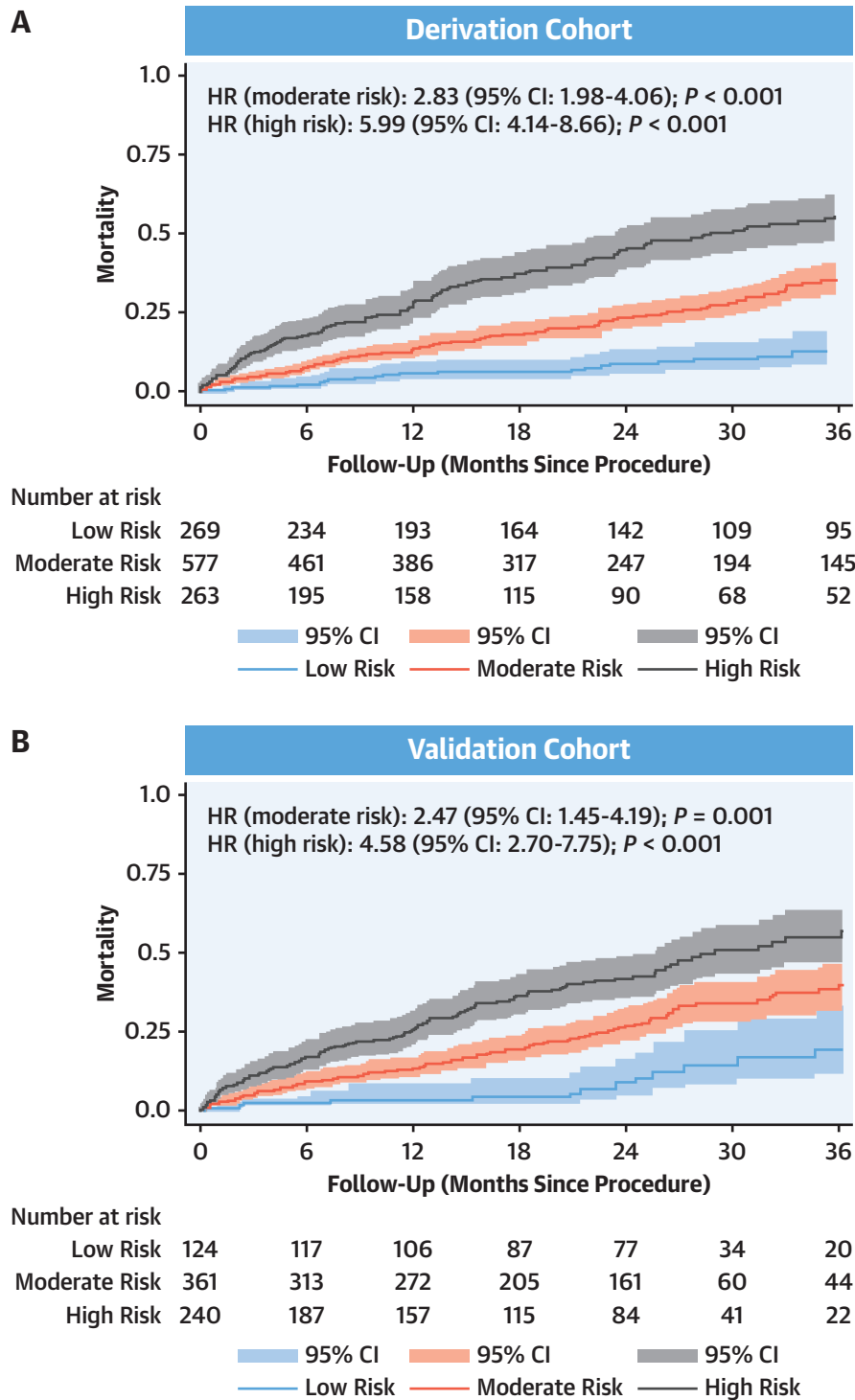
This study developed and validated the MitraScore, a simple bedside prediction tool that can be implemented to estimate the risk of mortality in patients undergoing TEER. This novel score showed a modest discrimination and a good calibration in both derivation and validation cohorts, using contemporary registries. The MitraScore not only allowed the stratification of the risk of death, but also the identification of patients with better NYHA functional class in follow-up and a greater probability of surviving without developing heart failure.

Estimation of postprocedural survival in patients undergoing TEER is challenging because of different MR etiologies, high clinical complexity, and large burden of comorbidities. Current evidence on this

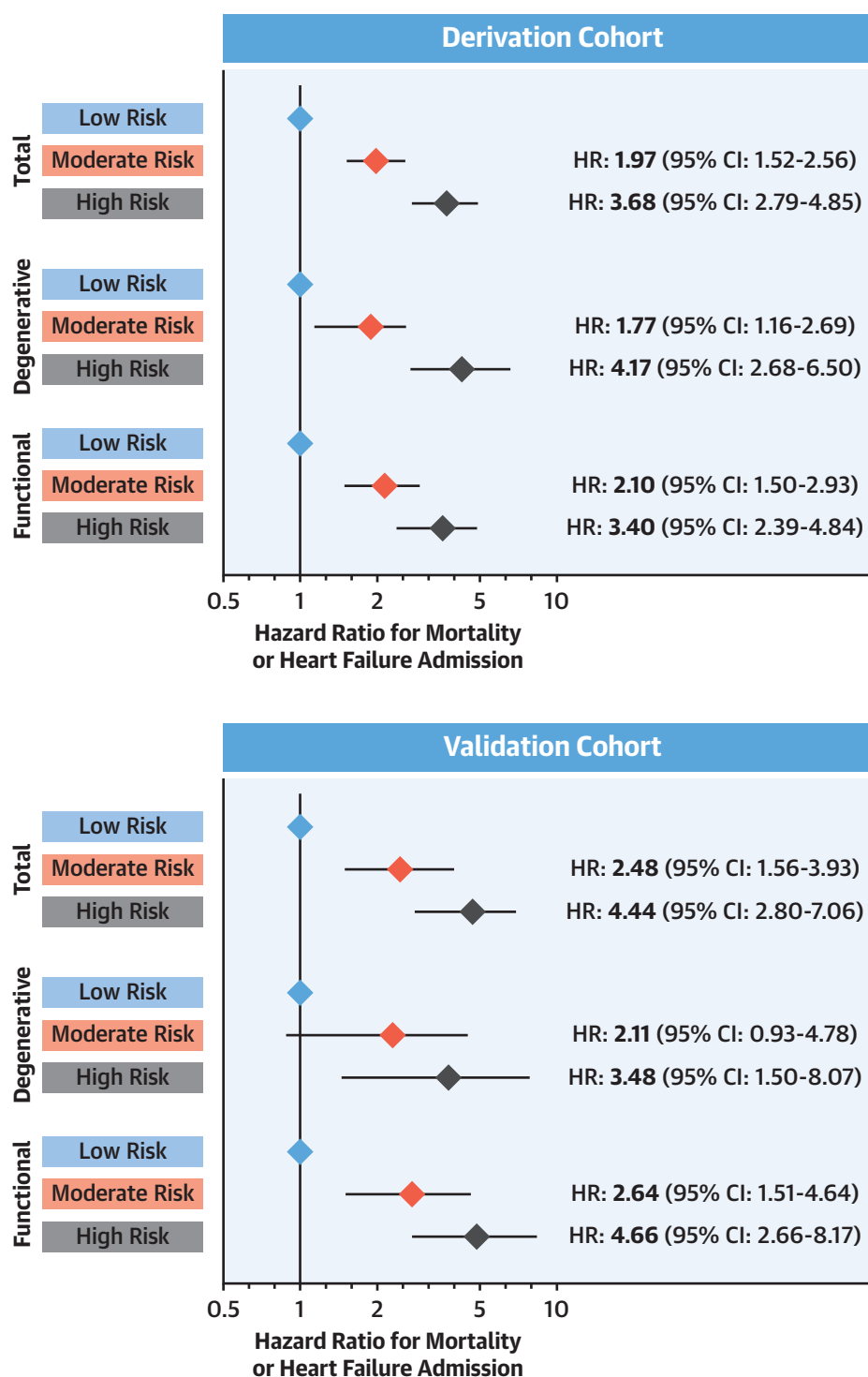
issue is scarce. Surgical risk scores (particularly, the EuroSCORE II and STS score) have systematically shown a relatively low accuracy in the prediction of acute and midterm mortality.<sup>14</sup> Other risk models proposed exclusively for TEER patients were derived from small patient cohorts, such as the GRASP (Getting Reduction of mitral InSufficiency by Percutaneous clip implantation) score, which is valuable but computationally complex, because it requires weighting terms for the predictor variables and cannot be implemented easily without computer assistance.<sup>20</sup> Likewise, a specific HF risk score, the Get With the Guidelines Heart Failure Risk Score, was also validated in patients undergoing TEER, with an optimal predictive ability (c-statistic 0.68), although requiring an application to calculate the score.<sup>15</sup> MitraScore overcomes these limitations by including 3 important issues: 1) the use of variables that can be easily ascertained beforehand when a patient with MR is evaluated for TEER; 2) the simple arithmetic sum of the number of variables present that constitutes the risk score can be calculated without the aid of a computer or electronic machine; and 3) the estimation of mortality risk with clinical variables before TEER. Although the discrimination of MitraScore is modest, its calibration and risk stratification are good. The ability to carry out an adequate risk stratification before the procedure with an easy-to-use score can facilitate widespread use in daily clinical practice.

We confirmed the role of well-known risk factors associated with mortality after TEER, such as age<sup>13</sup> or depressed left ventricular ejection fraction.<sup>13,21-23</sup> Similarly, comorbidities, like anemia,<sup>13,22</sup> chronic kidney disease,<sup>13,23</sup> chronic obstructive pulmonary disease,<sup>24</sup> or peripheral artery disease,<sup>13</sup> have been previously associated with mortality after TEER. Additionally, we featured the relevance of diuretic dose and the absence of RAS inhibitors in the treatment regimen (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or sacubitril-valsartan), which emerged as strong predictors of mortality in our score. High diuretic dose reflects the most advanced stages of heart failure and advanced functional classes, as a surrogate marker of poor prognosis.<sup>21</sup> Likewise, the association between no therapy with RAS inhibitors and mortality after TEER highlights the importance of optimal medical therapy in every patient undergoing TEER.<sup>25</sup> This feature is of special relevance when applying the score to secondary MR patients, where optimization of HF therapy has proven to be of utmost importance to maximize the benefits of the percutaneous repair.<sup>7,11</sup> In the near future, the addition of

**FIGURE 2** Mortality After Transcatheter Mitral Valve Repair According to MitraScore

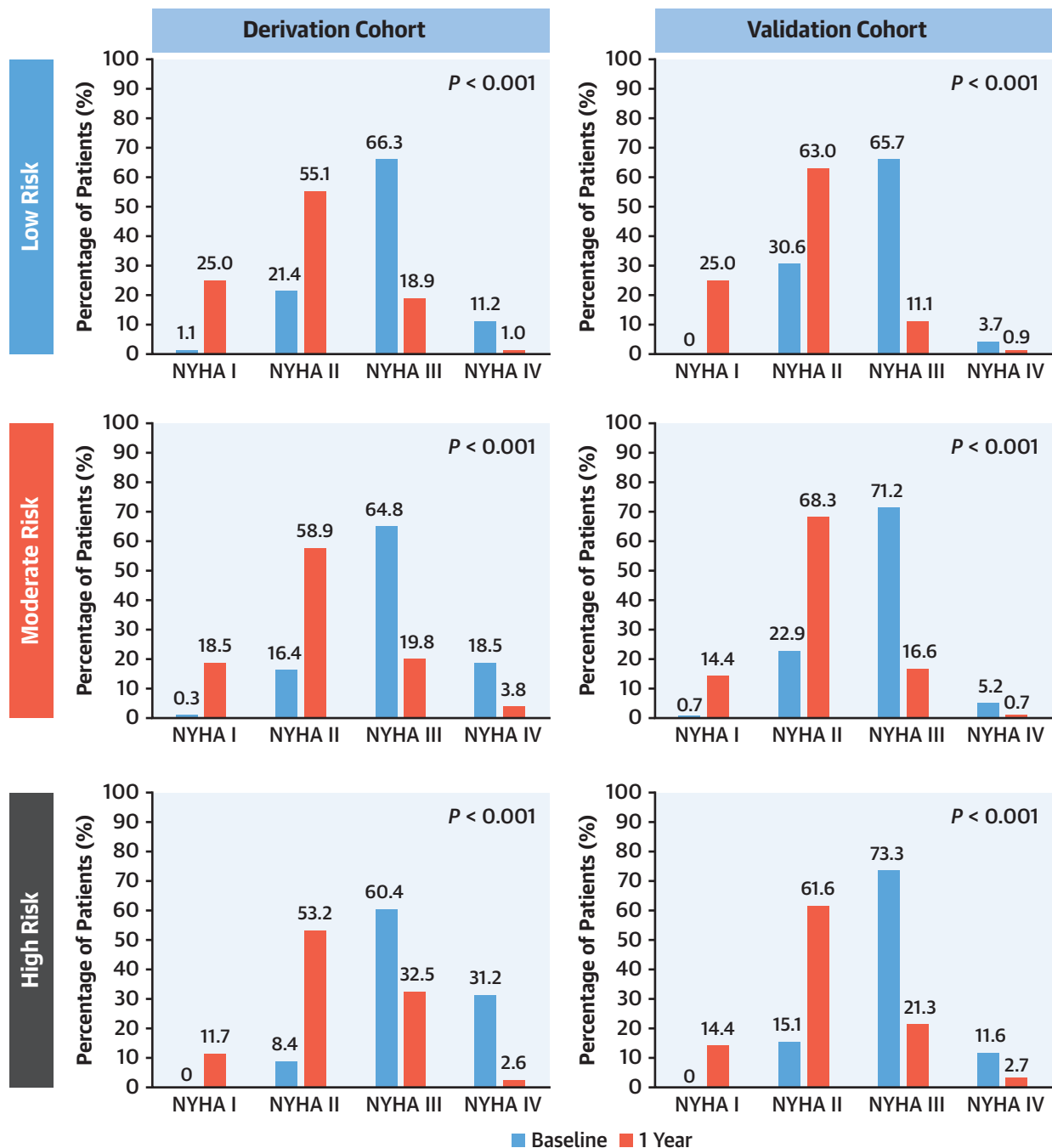


Follow-up mortality after stratifying for MitraScore Risk groups in both the derivation (A) and validation (B) cohorts. Patients were classified into 3 risk groups of MitraScore by tertiles: low-risk ( $\leq 25$ th percentile), moderate-risk (25-75th percentile), and high-risk ( $\geq 75$ th percentile).

**FIGURE 3** Risk of Mortality and/or Heart Failure Hospitalization According to MitraScore

Hazard ratio for the combined endpoint of mortality and/or hospitalization by heart failure after transcatheter mitral valve repair according to the MitraScore risk groups in both derivation and validation cohorts.

**FIGURE 4** Functional Class After Transcatheter Mitral Valve Repair According to MitraScore



Change in New York Heart Association (NYHA) functional class according to MitraScore risk groups in both derivation and validation cohorts. Red bars show baseline NYHA functional class, whereas blue bars show 1-year NYHA functional class.

functional/frailty parameters, or advanced imaging parameters (LV volumes, quantification of MR or right ventricular function), could provide a better estimation of those patients who would not benefit from

these procedures.<sup>26</sup> All of this should translate into improved patient selection for TEER, which in turn should be associated with both improved outcomes and a better cost-effectiveness ratio.

Our study represents an important step forward toward better and more objective risk estimation of TEER patients. The implementation of the MitraScore in clinical practice should help heart teams in the (commonly not easy) clinical decision-making process regarding the selection of transcatheter repair candidates. However, it is important to keep in mind that risk-prediction tools are developed in populations, not individuals. Although the risk-prediction tools may inform practitioners regarding the estimated likelihood of complications and CV events in a patient, each individual patient is unique and subject to many influences not measured or ascertained in clinical practice. Local practice referral patterns or practice style may influence average risks of patients being cared by an individual clinician. That is the reason for proposing the use of our MitraScore in addition to a thorough evaluation of the patient by the heart team. Those falling into a high-risk category might benefit from closer ambulatory follow-up to optimize medical and device-based therapy to prevent a negative effect on clinical status or quality of life. An interesting finding from our study is that the MitraScore was also associated with the functional class after TEER. As the MitraScore risk groups progressed (from low to high risk), the percentage of patients who reached NYHA functional class I-II decreased. Up to 1 in 4 patients in the high-risk group present NYHA functional class III-IV 1 year after the procedure. However, even in patients in the high-risk group, an improvement in functional status was observed after MitraClip implantation. This is important to inform the patient and family of when proceeding to TEER. Furthermore, future studies should determine the potential usefulness of using such MitraScore to predict clinical outcomes following this or other transcatheter mitral valve therapies.

**STUDY LIMITATIONS.** First, our study is based on 2 retrospective observational registries. Registries cannot replace randomized evidence and have the inherent limitation to be not completely controlled with the risk of under-reporting of events or complications. However, they adequately reflect real-life conditions. Second, the MIVNUT and Giotto registries were not industry-sponsored (which is also a strength of the registry), patient enrollment was on a voluntary basis, and no remuneration was paid. All baseline and in-hospital data were site-reported, and echocardiographic data were not core-laboratory adjudicated, and therefore of minor quality. Third, although our risk score predicts a sufficiently large

gradient of risk among the 3 risk groups, we acknowledge that event discrimination as continuous variable of our score was modest. The retrospective nature of the MIVNUT study may lead to a bias in patient selection, leading to the absence of statistical significance of certain echocardiographic variables. Emerging predictors for mortality, including frailty and advanced echo parameters, might help to improve the predictive ability, although they are not available for the present study. Fourth, the introduction of weighting factors for predictor variables or expansion of the list of predictor variables may lead to improvement in statistical measures of the predictive performance of the model (eg, c-statistic), but this is likely to occur at the cost of a loss of simplicity.

## CONCLUSIONS

The MitraScore score is a simple 8-item algorithm for the prediction of mortality in patients treated with TEER. In the context of a comprehensive clinical evaluation process, this tool might help to support clinical decision making. We believe that clinicians will find it simple to use and applicable to clinical practice, although prospective validation of this score in practice remains desirable.

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## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND

**PROCEDURAL SKILLS:** A risk score based on age  $\geq 75$  years, anemia, estimated glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup>, left ventricular ejection fraction  $< 40\%$ , peripheral artery disease, chronic obstructive pulmonary disease, high diuretic dose, and lack of therapy with RAS inhibitors accurately predicts mortality during follow-up of patients after percutaneous mitral valve repair.

**TRANSLATIONAL OUTLOOK:** Future research should assess whether specific interventions that target each component of the risk model can reduce the risk of mortality after percutaneous mitral valve repair.



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**KEY WORDS** mortality, score, transcatheter edge-to-edge mitral valve repair

**APPENDIX** For a supplemental figure and tables, please see the online version of this paper.







